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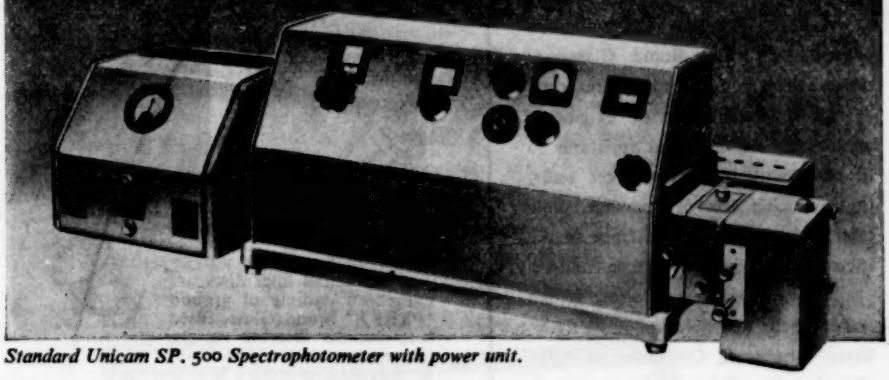

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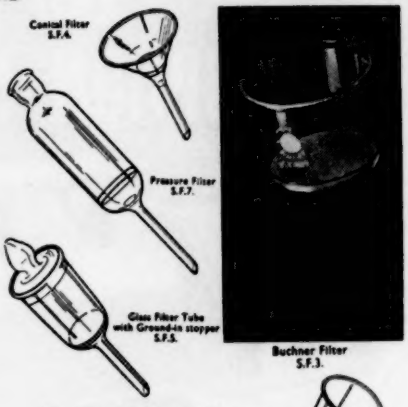

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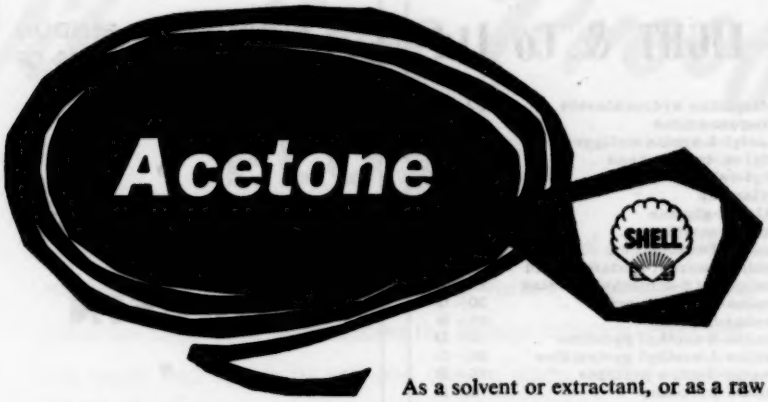

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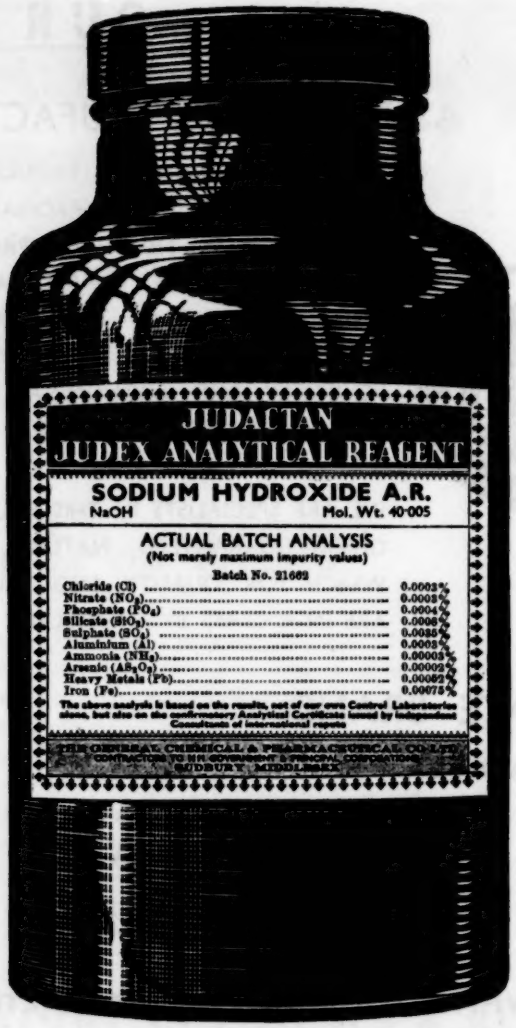
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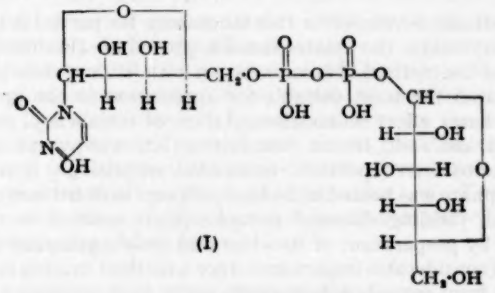
703. *Nucleotides. Part XV.* A Synthesis of Uridine-5′ Pyrophosphate, a Breakdown Product of the Coenzyme "Uridine-diphosphate-glucose."*

By N. Anand, V. M. Clark, R. H. Hall, and A. R. Todd.

Uridine-5′ pyrophosphate has been synthesised by condensing 2′ : 3′-*iso*propylidene 5′-iodo-5′-deoxyuridine with silver tribenzyl pyrophosphate and subsequently removing the protecting groups. The product, isolated as its barium salt, is identical with the " uridine diphosphate " obtained as a breakdown product of the naturally occurring coenzyme UDPG.

In course of the work described use has been made of the observation that lithium chloride removes two benzyl groups from fully esterified pyrophosphates.

The initial step in the utilisation of galactose by animals has been shown to involve a phosphorylation by adenosine triphosphate catalysed by galactokinase (Caputto, Leloir, and Trucco, *Enzymologia*, 1948, **12**, 350; Wilkinson, *Biochem. J.*, 1949, **44**, 460) to yield galactose-1 phosphate. In 1950 Caputto, Leloir, Cardini, and Paladini (*J. Biol. Chem.*, 1950, **184**, 333) isolated from baker's yeast the coenzyme of the system (galactowaldenase) which brings about the subsequent conversion of galactose-1 phosphate into glucose-1 phosphate, and on the basis of their elegant degradative studies they advanced for it structure (I) and named it " uridine-diphosphate-glucose," a term commonly abbreviated to UDPG. The evidence for this structure may be summarised briefly as follows. UDPG, which has no reducing properties, yielded on hydrolysis uridine (1 mol.), D-glucose (1 mol.), and phosphoric acid (2 mols.). Titration showed the presence of two primary phosphoryl dissociations only and gentle acid hydrolysis yielded a " uridine diphosphate," which was evidently a pyrophosphate since it contained one acid-labile phosphate residue; removal of the acid-labile phosphate left a simple nucleotide which was subsequently shown to be uridine-5′ phosphate by direct comparison with a synthetic specimen prepared in this laboratory (Paladini and Leloir, private communication; see also *Biochem. J.*, 1952, **51**, 426). It was clearly desirable that the uridine diphosphate obtained from UDPG should be identified in order to confirm structure (I) and accordingly we undertook the synthesis of uridine-5′ pyrophosphate (V).

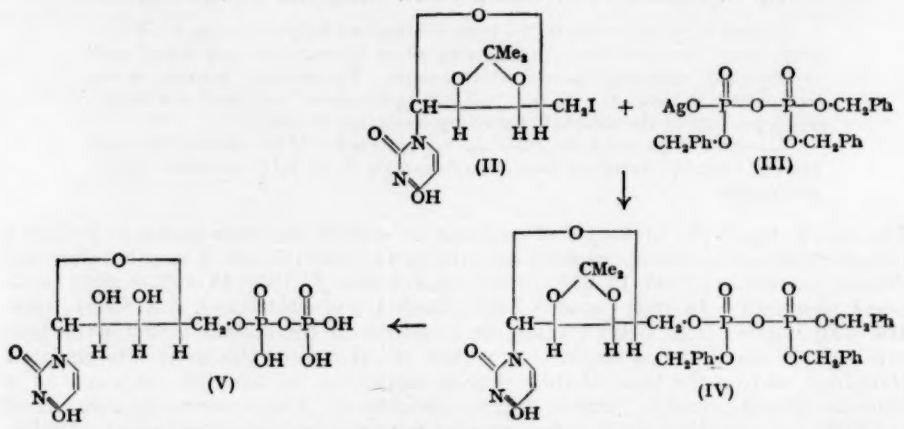


(I)

A synthesis of adenosine-5′ pyrophosphate was readily achieved by Baddiley and Todd (Part I, *J.*, 1947, 648) by condensation of silver adenosine-5′ benzyl phosphate with dibenzyl chlorophosphonate and subsequent removal of protecting benzyl groups. This method was found to be unsuitable for the preparation of the analogous uridine-5′ pyrophosphate since the acidic nature of the uracil residue gave rise to complications in the use of silver salts of uridine phosphate derivatives. As an alternative it was decided to attempt a synthesis by condensing the known 2′ : 3′-*iso*propylidene 5′-iodo-5′-deoxyuridine (II) (Levene and Tipson, *J. Biol. Chem.*, 1934, **106**, 113) with silver tribenzyl pyrophosphate;

* Part XIV, *J.*, 1952, 2721.

that the former compound reacted with silver dibenzyl phosphate to give a product from which uridine-5′ phosphate could be obtained by removal of protecting groups was known from earlier work of Dr. J. Davoll in this laboratory. When a benzene solution of the above 5′-iodo-derivative was heated with silver tribenzyl pyrophosphate (III) (Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815), silver iodide was precipitated and 2′ : 3′-*iso*propylidene

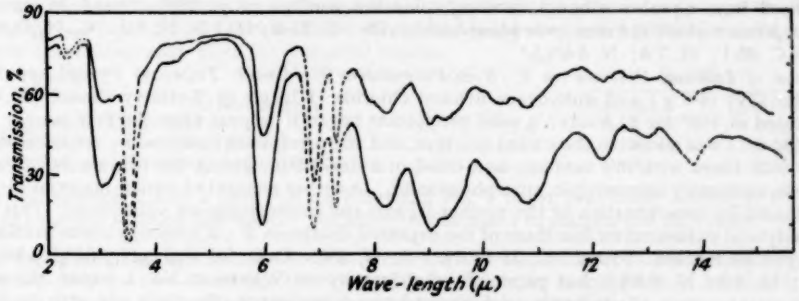


uridine-5′ tribenzyl pyrophosphate (IV) was obtained in good yield. Attempts to remove all the protecting benzyl groups from this product were unsuccessful. On catalytic hydrogenation by using either platinum or palladium catalysts very little hydrogen uptake occurred. Failures of this type have been from time to time encountered by us in the hydrogenolysis of benzyl esters of the phosphoric acids and we attribute them to traces of catalyst poisons derived from intermediates used in their preparation. Since fully esterified pyrophosphates are rather unstable it was decided to effect a partial debenzylation of the product so as to give an acidic substance which would be at once more stable and would lend itself to purification by salt formation. In this way any catalyst poison might be eliminated and hydrogenolysis of residual benzyl groups might then be readily accomplished.

Of the various methods developed in this laboratory for partial debenzylation of esters of the phosphorus oxy-acids, the quaternisation procedure (Baddiley, Clark, Michalski, and Todd, *loc. cit.*) and the method of anionic fission with lithium chloride (Clark and Todd, *J.*, 1959, 2030) appeared the most suitable for application to the product (IV). It was known that tertiary bases effect monodebenzylation of tetrabenzyl pyrophosphate (Baddiley, Clark, Michalski, and Todd, *loc. cit.*) but debenzylation of pyrophosphates with lithium chloride has not hitherto been reported. Somewhat surprisingly it was found that when tetrabenzyl pyrophosphate was heated in 2-ethoxyethanol with lithium chloride, two benzyl groups were removed, yielding dibenzyl pyrophosphate isolated as its lithium salt and further characterised by preparation of its silver and *cyclo*hexylamine salts. This observation is, we believe, of considerable importance since a method causing simultaneous removal of two benzyl groups from pyrophosphate esters under mild conditions and without hydrogenation may be of value in synthetic studies on such coenzymes as cozymase; this aspect will be dealt with in a later paper. In the present case it was decided to apply the lithium chloride procedure to (IV). The product, obtained as a lithium salt, gave analytical values which were in fair agreement with the calculated values for a hydrated dilithium 2′ : 3′-*iso*propylidene uridine-5′ benzyl pyrophosphate, but paper chromatography indicated that it was contaminated with the salt of the corresponding acid which had lost the 2′ : 3′-*iso*propylidene residue. No attempt was made to separate the two components completely; the salt was subjected to hydrogenation in acid solution so as to cause simultaneous removal of the remaining benzyl group and the *iso*propylidene residue. The product, precipitated

as barium salt, was shown by paper chromatography to contain two components and a sample of barium uridine diphosphate prepared from natural UDPG and kindly supplied by Dr. L. Leloir showed exactly the same behaviour. One of the components—the minor one—was identical with uridine-5′ phosphate, evidently formed by some breakdown of the 5′-pyrophosphate. For final purification the barium salt was subjected to precipitation under controlled pH conditions. Barium uridine-5′ pyrophosphate was precipitated at pH 5·6, leaving barium uridine-5′ phosphate in solution; the latter was precipitated at pH 9. By a final reprecipitation the monobarium salt of uridine-5′ pyrophosphate was obtained and was shown to be identical in composition, chromatographic behaviour, and infra-red spectrum (see Figure), with uridine diphosphate of natural origin obtained by a similar purification of Dr. Leloir's material. The product of mild acid hydrolysis of UDPG is thus shown to be uridine-5′ pyrophosphate (V), a finding which lends substantial support to the formulation of the coenzyme as (I).

The reaction between 2′ : 3′-*iso*propylidene 5′-iodo-5′-deoxyuridine and salts of phosphoric and polyphosphoric acids employed in this paper represents a method of nucleotide synthesis which has not hitherto been employed. Although capable of further exploitation



Upper curve : Natural "uridine diphosphate."
Lower curve : Synthetic uridine-5′-pyrophosphate.

it should be mentioned that its scope is limited, in so far as the ease with which *cyclo*-nucleoside salts are formed from 5′-substituted adenosine and cytidine derivatives (Clark, Todd, and Zussman, *J.*, 1951, 2952) precludes its use with derivatives of these nucleosides, unless some convenient means (*e.g.*, *N*-acylation) could be found to reduce their basicity. The reactivity of the 5′-iodo-5′-deoxyuridine derivative in replacement reactions is rather surprising. During the past five or six years various workers in this laboratory have examined anionic replacement reactions of this general type with a variety of carbohydrate derivatives in which the substituent to be replaced was on the terminal carbon atom. Derivatives of the open-chain *aldehydo*-sugars always reacted readily, whereas those containing a lactol ring (*e.g.*, methylribofuranoside derivatives), were so sluggish in reaction as to make them, for practical purposes, of little value. 2′ : 3′-*iso*Propylidene 5′-iodo-5′-deoxyuridine, however, is anomalous in that it shows a degree of reactivity comparable with that of the *aldehydo*-sugar derivatives.

Experimental

2′ : 3′-Iso*propylidene Uridine-5′ Tribenzyl Pyrophosphate*.—A solution of 2′ : 3′-*iso*propylidene 5′-iodo-5′-deoxyuridine (3·68 g.; Levene and Tipson, *loc. cit.*) in dry benzene (80 c.c.) was refluxed for 15 minutes with freshly prepared silver tribenzyl pyrophosphate (5·15 g.; Baddiley, Clark, Michalski, and Todd, *loc. cit.*). Silver iodide (2·14 g.), which began to be precipitated within 1 minute, was filtered off and the benzene solution evaporated. The yellowish residual gum was dissolved in dry acetone and filtered through Hyflo Supercel, and the filtrate evaporated, giving the *product* as a colourless resin (6·5 g., 98%) (Found, in material dried for 24 hours at room temperature/0·1 mm. over phosphoric oxide: C, 54·9; H, 5·3; N, 3·6. $C_{33}H_{36}O_{12}N_2P_2$ requires C, 55·4; H, 5·1; N, 3·9%).

Action of Lithium Chloride on Tetrabenzyl Pyrophosphate.—Tetrabenzyl pyrophosphate (1·115 g.; Atherton and Todd, *J.*, 1947, 674) and anhydrous lithium chloride (355 mg., 4 mols.), dissolved in freshly distilled 2-ethoxyethanol (10 c,c.). were heated at 100° for 45 minutes. A colourless crystalline solid began to separate within 5 minutes of the commencement of heating and a marked odour of benzyl chloride developed. The mixture was cooled and the precipitated *dilithium dibenzyl pyrophosphate* (713 mg., 93%) was collected, washed with 2-ethoxyethanol and with ether, and finally recystallised from aqueous acetone from which it separated as a hydrate in colourless fine needles, m.p. 250° (Found, in material dried for 3 hours at 80°/20 mm. over phosphoric oxide: C, 43·6; H, 4·0. $C_{14}H_{14}O_7P_2Li_2,H_2O$ requires C, 43·3; H, 4·1%).

Disilver dibenzyl pyrophosphate was prepared as a white powder from the above lithium salt by addition of silver nitrate to its aqueous solution (Found: Ag, 37·8. $C_{14}H_{14}O_7P_2Ag_2$ requires Ag, 37·9%).

When a stream of hydrogen sulphide was passed though a suspension of the above silver salt (0·784 g.) in chloroform (25 c.c.) for 20 minutes and precipitated silver sulphide was filtered off, a solution was obtained which, when evaporated under reduced pressure, yielded dibenzyl pyrophosphate (457 mg.) as a colourless oil which appeared not to crystallise readily. It was dissolved in ether (10 c.c.)–acetone (3 c.c.), and *cyclo*hexylamine (300 mg.) in ether (10 c.c.) was added. The precipitated *di*(cyclo*hexylammonium*) *dibenzyl pyrophosphate* (530 mg.) was recrystallised from aqueous ethanol, forming colourless needles, m. p. 228° (Found, in material dried for 5 hours at 80°/20 mm. over phosphoric oxide: C, 55·9; H, 7·5; N, 5·0. $C_{26}H_{42}O_7N_2P_2$ requires C, 56·1; H, 7·6; N, 5·0%).

Action of Lithium Chloride on 2′ : 3′-iso*Propylidene Uridine-5′ Tribenzyl Pyrophosphate.*—The ester (IV) (6·5 g.) and anhydrous lithium chloride (1·75 g.) in 2-ethoxyethanol (80 c.c.) were heated at 100° for 2½ hours; a solid precipitate began to appear after the first hour. Dry ether (190 c.c.) was added to the cooled solution, and the precipitate collected by centrifugation, washed four times with dry acetone, and dried in a desiccator, giving the lithium salt (2·5 g.) as a white, extremely hygroscopic, amorphous solid. A futher amount of similar material (0·7 g.) was obtained by concentration of the mother-liquors and re-precipitation with ether. This salt gave analytical values rather like those of the expected dilithium 2′ : 3′-*iso*propylidene uridine-5′ benzyl pyrophosphate (Found: C, 39·3; H, 4·7; N, 4·0. Calc. for $C_{19}H_{22}O_{12}N_2P_2Li_2,2H_2O$: C, 39·2; H, 4·5; N, 4·8%), but paper chromatography on Whatman No. 1 paper, the *tert.*-butanol–water system (4 : 1) being used, showed two components, the main one with R_F 0·56, the other with R_F 0·32; both components absorbed ultra-violet light and contained phosphorus but, when sprayed with neutral periodate followed by Schiff's reagent (Buchanan, Dekker, and Long, *J.*, 1950, 3162), only the slower-moving component gave a positive reaction. Similar results were obtained on using as solvent system *iso*propyl alcohol–1% ammonium sulphate (2 : 1) on Whatman No. 1 paper previously soaked in 1% ammonium sulphate solution and dried; the two components had R_F values 0·87 and 0·75 respectively. The faster-moving component was in all preparations present in much the greater amount and is evidently 2′ : 3′-*iso*propylidene uridine-5′ benzyl pyrophosphate. The quantity of the other varied in different preparations but in the sample analysed appeared to be *ca.* 10%; from its behaviour with periodate it can be regarded as uridine-5′ benzyl pyrophosphate, some hydrolysis of the *iso*propylidene group having occurred during the debenzylation reaction.

Uridine-5′ Pyrophosphate.—The above lithium salt (2·5 g.) was dissolved in water (150 c.c.), and 0·1N-hydrochloric acid (10 c.c.) was added. The weakly acid solution was hydrogenated for 24 hours at room temperature, a 10% palladised charcoal catalyst (2 g.) being used. The mixture was filtered, and the filtrate neutralised to pH 7 with barium hydroxide and concentrated to small bulk (30 c.c.). The pH was then brought to 1·0 with hydrochloric acid to ensure complete solution, barium bromide (1·15 g) added, and the pH raised to 3·0 with barium hydroxide. Barium phosphate (0·34 g.) was removed by filtration, the pH raised to 8·5 with barium hydroxide, and ethanol (80 c.c.) added. The precipitated crude barium uridine-5′ pyrophosphate (1·72 g.) was collected by centrifugation, washed with acetone, and dried. This crude salt behaved on paper chromatography with *iso*propyl alcohol–1% ammonium sulphate (2 : 1) exactly like a specimen of " uridine diphosphate " supplied by Dr. Leloir. It contained a major component of R_F 0·27 and a minor one of R_F 0·45. Both contained phosphorus, absorbed ultra-violet light, and gave positive reactions with the periodate spray. The minor component (about 25% of the total) was identified as uridine-5′ phosphate by direct comparison on a paper chromatogram with an authentic specimen (R_F 0·45).

The crude barium salt (200 mg.) was dissolved in hydrobromic acid (3·5 c.c.; 0·1 N) and the pH brought to 3·5 with barium hydroxide (0·3N). A slight precipitate of barium phosphate

was filtered off and washed with water (1·25 c.c.). The combined filtrate and washings were brought to pH 5·6 with barium hydroxide, and ethanol (8 c.c.) was added. The precipitate (147 mg.) was collected by centrifugation and washed with acetone, then with ether, and dried. This procedure was repeated three times more and, in order to ensure that only the monobarium salt was present in the final product, a sample (25 mg.), before analysis, was dissolved in hydrobromic acid (1 c.c.; 0·01N) and filtered through sintered glass, the filter being washed with water (0·5 c.c.). Ethanol (4 c.c.) was added and the white amorphous precipitate of *monobarium uridine-5′ pyrophosphate* was collected, washed with ethanol, then ether, and dried at room temperature/20 mm. (Found: C, 18·2; H, 3·3; N, 4·4; P, 10·5. $C_9H_{12}O_{12}N_2P_2Ba,3H_2O$ requires C, 18·2; H, 3·0; N, 4·7; P, 10·5%).

From the mother-liquors from the initial pyrophosphate precipitation at pH 5·6 barium uridine-5′ phosphate (18 mg.) was obtained by increasing the pH to 9 with barium hydroxide.

Comparison of Synthetic Barium Uridine-5′ Pyrophosphate with Barium "Uridine Diphosphate" of Natural Origin.—The sample of barium "uridine diphosphate" supplied by Dr. Leloir was freed from contaminating barium uridine-5′ phosphate (*ca.* 10%) by precipitation at pH 5·6 and final purification as indicated above for the synthetic product; it was thus obtained as a white amorphous powder (Found: C, 18·2; H, 3·2; P, 10·6. Calc. for $C_9H_{12}O_{12}N_2PBa,3H_2O$: C, 18·2% H, 3·0; P, 10·5%).

The purified natural product and the synthetic pyrophosphate gave infra-red spectra which were identical (Nujol mulls; Perkin–Elmer Model 21, double-beam instrument). Comparison by paper chromatography gave the following results:

Solvent system	R_P values: Natural	Synthetic
1, Bu^nOH–H_2O–AcOH (60 : 30 : 20)	0·16	0·16
2, Pr^iOH–1% aq. $(NH_4)_2SO_4$ (60 : 40)	0·54	0·54
3, Pr^iOH–1% aq. $(NH_4)_2SO_4$–AcOH (45 : 35 : 20)	0·40	0·43

Solvent systems 2 and 3 were run on Whatman No. 1 paper previously soaked in 1% ammonium sulphate solution and dried. No attempt was made to standardise R_P values.

We are grateful to the Royal Commissioners for the Exhibition of 1851 for an Overseas Scholarship held by one of us (R. H. H.), to Dr. L. Leloir for a specimen of barium uridine diphosphate, and to Roche Products Ltd. for grants and gifts of material.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, April 30th*, 1952.]

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704. *Nucleotides. Part XVI.* Ribonucleoside-5′ Phosphites. A New Method for the Preparation of Mixed Secondary Phosphites.*

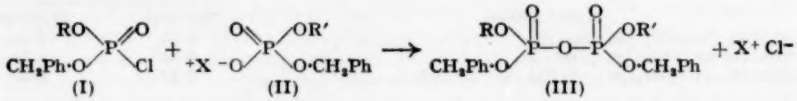
By N. S. CORBY, G. W. KENNER, and A. R. TODD.

Solutions of *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride (VII), prepared by the interaction of a salt of monobenzyl phosphite and diphenyl chlorophosphonate or tetraphenyl pyrophosphate, react with alcohols in the presence of base, yielding alkyl benzyl phosphites. The constitutions of 2′ : 3′-*iso*propylidene uridine-5′ and 2′ : 3′-*iso*propylidene adenosine-5′ benzyl phosphites, prepared in this way, have been demonstrated by conversion of these esters into the corresponding *p*-bromobenzylaminophosphonates and benzyl hydrogen phosphates.

THE key to successful synthesis in the polynucleotide and the nucleotide coenzyme fields clearly lies in the development of methods for linking together dissimilar molecules (in particular nucleoside molecules) through phosphate or pyrophosphate residues, and such methods have been sought in an extensive series of investigations in this laboratory during recent years. In many respects the two problems overlap and it seems probable that any method suitable for one might, with certain modifications, be applied to the other. In considering the problem of the synthesis of dinucleoside pyrophosphates, a solution to which would give a route to the nucleotide coenzymes (*e.g.*, cozymase, flavin adenine dinucleotide), several possibilities are apparent. One of them involves exchange reactions between

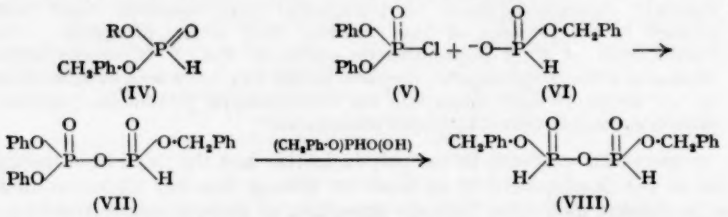
* Part XV, preceding paper.

a nucleoside pyrophosphate, or a mixed anhydride of a nucleotide with some stronger acid, and the salt of a monoester of a nucleotide, and model experiments on the preparation of simple pyrophosphates by this method have already been reported (Corby, Kenner, and Todd, *J.*, 1952, 1234). A second route might utilise the reaction between a 5′-halogeno-5′-deoxynucleoside and a nucleoside dibenzyl pyrophosphate. A model synthesis indicating the possibility of realising such a reaction exists in the synthesis of uridine-5′ pyrophosphate from 5′-iodo-5′-deoxyuridine already described (Part XV, Anand, Clark, Hall, and Todd, preceding paper); this route would, of course, only be applicable in a limited number of cases since adenosine and cytidine undergo conversion into *cyclo*nucleoside derivatives when attempts are made to prepare from them the corresponding 5′-iodo-compounds (Part VIII, Clark, Todd, and Zussman, *J.*, 1951, 2952). The third and most obvious method would be to utilise the well-known and almost universally applied route to pyrophosphates in which a dialkyl (or diaryl) chlorophosphonate is treated with the salt of a diester of phosphoric acid. In practice this would mean reaction of a nucleoside benzyl chlorophosphonate (I; R = nucleoside residue) with the salt of a nucleoside benzyl hydrogen phosphate (II; R′ = nucleoside residue) to give a tetraester (III) of pyrophosphoric acid, from which the protecting benzyl groups could subsequently be removed. Hitherto this method could not be applied since it was not possible to prepare nucleoside benzyl chlorophosphonates (cf. Mason and Todd, *J.*, 1951, 2267). Experiments directed to the solution of the latter problem form the subject of the present communication.



(I) (II) (III)

The most satisfactory method for the preparation of dialkyl or diaralkyl chlorophosphonates is the chlorination of diesters of phosphorous acid, but before this method could be explored in the present instance it was necessary to have available nucleoside benzyl phosphites (IV; R = nucleoside residue). Such compounds have not hitherto been prepared and, indeed, very little is known about mixed secondary phosphites of any type (cf. Kosolapoff, *J. Amer. Chem. Soc.*, 1951, **73**, 4989); we therefore sought a general method for their preparation. In experiments bearing on the exchange reactions of mixed anhydrides of diesters of phosphoric acid (Corby, Kenner, and Todd, *loc. cit.*) it had been consistently observed that, in reaction with an amine, these mixed anhydrides always gave the aminophosphonate corresponding to the weaker of the two parent acids from which the anhydride was derived; thus, dibenzyl diphenyl pyrophosphate always yielded with ammonia dibenzyl aminophosphonate. It therefore seemed to us probable that a mixed anhydride (VII) of monobenzyl phosphite and diphenyl phosphate would prove a suitable reagent for the preparation of mixed secondary phosphites since it should, by analogy with



(IV) (V) (VI) (VII) (VIII)

the pyrophosphates, react with an alcohol (ROH) in presence of a tertiary base to form the ester (IV) of the weaker acid (phosphorous acid). It may be mentioned that in the absence of a systematic nomenclature for polyacids of the phosphorus series the naming of (VII) presents some difficulty. For the present at any rate it would seem simplest to use a " mixed anhydride " form of nomenclature for compounds of this and similar types; (VII) would thus be named *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride.

The mixed anhydride (VII) was first prepared by allowing diphenyl chlorophosphonate

(V) to react with monobenzyl phosphite (VI) (Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815). The product was a thick resin which, like many of the anhydrides of oxy-acids of phosphorus, was unstable to moisture or heat, or to ammonia and amines generally. Purification by distillation was impossible and so the product was always used directly in the crude state. It was not analysed since in any case elementary analysis of mixed anhydrides has little value in view of their marked tendency to disproportionate, giving mixtures of the corresponding symmetrical substances (cf. Corby, Kenner, and Todd, *loc. cit.*). Indeed the only satisfactory evidence for the identity of any such anhydride is the demonstration that it can be converted in good yield into a product whose structure is known and which could only have been produced from the anhydride in question. This method was employed in the present instance. The anhydride (VII) reacted with benzyl alcohol in presence of one equivalent of 2 : 6-lutidine, giving the expected dibenzyl phosphite, easily identified by conversion into the crystalline dibenzyl aminophosphonate (Atherton and Todd, *J.*, 1947, 674). The yield of dibenzyl phosphite was some 61%, calculated on the assumption that the starting material was pure *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride (VII). The mixed anhydride (VII) could also be prepared by allowing tetraphenyl pyrophosphate to react with a salt of monobenzyl phosphite, but the purity of the product was evidently lower since the yield of dibenzyl phosphite obtainable from it by reaction with benzyl alcohol was only 46%, calculated on the above basis.

That the reagent (VII) could be used satisfactorily for the preparation of mixed secondary phosphites was demonstrated by treating it with *p*-nitrobenzyl alcohol in presence of one equivalent of 2 : 6-lutidine. The product, benzyl *p*-nitrobenzyl phosphite (IV; R = $NO_2 \cdot C_6H_4 \cdot CH_2$), was not isolated as such but was chlorinated directly and the crude chlorophosphonate produced treated directly (*a*) with aqueous sodium hydrogen carbonate, yielding benzyl *p*-nitrobenzyl hydrogen phosphate, and (*b*) with *cyclo*hexylamine, giving benzyl *p*-nitrobenzyl *cyclo*hexylaminophosphonate. Attention was next turned to the preparation of nucleoside benzyl phosphites. From the reaction between the mixed anhydride (VII) and 2′ : 3′-*iso*propylidene uridine in acetonitrile solution in presence of base, a resinous product was obtained. This appeared homogeneous on inspection of its paper chromatograms in ultra-violet light, but the molybdate reagent (Hanes and Isherwood, *Nature*, 1949, **164**, 1107) revealed the presence of a second more mobile phosphorus-containing substance. Owing to contamination with this impurity, the nature of which is discussed below, the nitrogen analysis of the resin was lower than that calculated for 2′ : 3′-*iso*propylidene uridine-5′ benzyl phosphite (IV; R = 2′ : 3′-*iso*propylidene uridine-5′ residue), but the evidence of its reactions left no doubt that it was essentially this substance. It appeared to be stable in cold chloroform solution towards water and saturated aqueous potassium hydrogen sulphate or sodium hydrogen carbonate; it was, however, very unstable towards dilute acids or alcoholic ammonia, the phosphite group undergoing hydrolysis. For identification it was brought into reaction with carbon tetrachloride and *p*-bromobenzylamine, a compound having the composition and behaviour of 2′ : 3′-*iso*propylidene uridine-5′ benzyl *p*-bromobenzylaminophosphonate being obtained in good yield. When equimolecular proportions of nucleoside, base, and mixed anhydride were used in its preparation the yield of 2′ : 3′-*iso*propylidene uridine-5′ benzyl phosphite was only moderate. A series of experiments was made, varying the quantities of the individual reactants, and it was finally established that optimum yields were obtained when the proportion nucleoside : base : mixed anhydride was 1 : 2 : 2. Reaction was usually complete in 2—3 hours but no drop in yield was noticed if the reaction mixture was kept overnight. When the same reaction was carried out with 2′ : 3′-*iso*propylidene adenosine in place of the corresponding uridine derivative, 2′ : 3′-*iso*propylidene adenosine-5′ benzyl phosphite (IV; R = 2′ : 3′-*iso*propylidene adenosine-5′ residue) was obtained as a hygroscopic glass very similar in properties to the uridine analogue; it could, however, be freed from the non-nitrogenous impurity by precipitation from benzene with *cyclo*hexane, being obtained as an amorphous solid of the correct composition. Treated with carbon tetrachloride and *p*-bromobenzylamine it gave the expected 2′ : 3′-*iso*propylidene adenosine-5′ benzyl *p*-bromobenzylaminophosphonate.

These results were encouraging but, in order to establish that the nucleoside derivatives obtained really were phosphites of type (IV), it was necessary to show that they could be converted into the related phosphates accessible by well-established procedures. This entailed the preparation from the phosphites of the corresponding chlorophosphonates, products which would be in any case required if the ultimate object of the investigation—the preparation of dinucleoside pyrophosphates or dinucleoside phosphates—was to be achieved. A satisfactory procedure for this purpose was devised by Mr. F. J. Weymouth (see Kenner, Todd, and Weymouth, succeeding paper) in which chlorination of a secondary phosphite is carried out in neutral solution with *N*-chlorosuccinimide. This reagent evidently converted 2′ : 3′-*iso*propylidene uridine-5′ benzyl phosphite into 2′ : 3′-*iso*propylidene uridine-5′ benzyl chlorophosphonate, since, when it was shaken with aqueous sodium hydrogen carbonate solution and the aqueous solution was acidified, the product gave 2′ : 3′-*iso*propylidene uridine-5′ benzyl hydrogen phosphate, an amorphous solid with the same R_F value as material prepared by Mr. S. M. H. Christie from 2′ : 3′-*iso*propylidene uridine-5′ dibenzyl phosphate (Michelson and Todd, *J.*, 1949, 2476) by debenzylation with 4-methylmorpholine (Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815). On further treatment with acid this material gave crystalline uridine-5′ benzyl hydrogen phosphate having the correct composition and consumption of periodate. In a similar manner amorphous 2′ : 3′-*iso*propylidene adenosine-5′ benzyl hydrogen phosphate and crystalline adenosine-5′ benzyl hydrogen phosphate were prepared from the correspondng phosphite and compared directly with authentic specimens.

The phosphorus-containing impurity, which did not absorb ultra-violet light, evidently did not interfere greatly with use of the nucleoside phosphites, but nevertheless its nature was of interest. A plausible hypothesis was that it was dibenzyl pyrophosphite (VIII) produced by attack of the anion of monobenzyl phosphite on the mixed anhydride (VII), during its preparation. This symmetrical anhydride (VIII) might have sufficiently low reactivity to survive washing with aqueous solutions of potassium hydrogen sulphate and sodium hydrogen carbonate. The reaction between two equivalents of monobenzyl triethylammonium phosphite and one of diphenyl chlorophosphonate should have led to (VIII) and, in fact, a small amount of oil remained after washing of the benzene solution with water and aqueous sodium hydrogen carbonate solution. This oil was, however, dibenzyl phosphite (IV; R = CH_2Ph). Moreover, when the washing with sodium hydrogen carbonate solution was omitted, a larger quantity of neutral oil was obtained, which developed acidity when kept at room temperature. We therefore conclude that dibenzyl pyrophosphite (VIII) is slowly transformed into dibenzyl phosphite and, presumably, metaphosphorous acid. Mixed secondary phosphites (IV) prepared by the method described here will thus always tend to be contaminated with dibenzyl phosphite, since the production of some (VIII) in the preparation of (VII) cannot be avoided. Likewise the reaction mixture in the preparation of (VIII) probably contained some (VII) which was destroyed by washing with water.

We consider that these experiments establish that derivatives of the ribonucleoside-5′ benzyl phosphites can be prepared through the agency of *OO*-diphenylphosphoric *O*-benzylphosphorous anhydride, and that by chlorination with *N*-chlorosuccinimide the corresponding nucleoside benzyl chlorophosphonates are produced from them. The accessibility of such chlorophosphonates should open up a number of routes to both phosphates and polyphosphates containing one or more nucleoside residues, and experiments designed to realise such routes will be reported in later papers.

Experimental

All m. p.s are corrected. Monobenzyl phosphite was prepared as a pale yellow thick oil by acidifying cold aqueous solutions of its ammonium salt (Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815) with dilute hydrochloric acid, extracting the mixture with chloroform, and evaporating the dried extract. It is stable in a nitrogen atmosphere but slowly decomposes when exposed to air for several days.

O-Benzylphosphorous OO-Diphenylphosphoric Anhydride (VII).—*Method* 1. Monobenzyl phosphite (0·195 g., 1 mol.) and diphenyl chlorophosphonate (0·24 c.c., 1 mol.) were dissolved

in dry benzene (15 c.c.). The solution, from which air and moisture were excluded, was stirred magnetically and a solution of anhydrous pyridine (0·09 c.c., 1 mol.) in dry benzene (5 c.c.) was gradually added. Pyridine hydrochloride began to separate after 2—3 minutes and after being stirred for 3 hours the mixture was filtered. No attempt was made to isolate the mixed anhydride (in other experiments it was obtained as an unstable resin by evaporating the solution) but its presence was demonstrated in the following way. Benzyl alcohol (0·12 c.c., 1 mol.) and 2 : 6-lutidine (0·13 c.c., 1 mol.) were added to the solution which was set aside at room temperature overnight, then washed with water, saturated aqueous sodium hydrogen carbonate, and saturated aqueous potassium hydrogen sulphate solutions, and finally dried (Na_2SO_4) and evaporated. The residue was dissolved in dry carbon tetrachloride, and gaseous ammonia passed through the solution for 20 minutes. Ammonium chloride (60 mg.) was removed by filtration and the filtrate concentrated to small bulk, whereupon dibenzyl aminophosphonate separated, having m. p. and mixed m. p. 101—103° (0·191 g., 61%).

Method 2. Monobenzyl phosphite (0·174 g., 1 mol.) was dissolved in dry methyl cyanide (10 c.c.), and 2 : 6-lutidine (0·115 c.c., 1 mol.) was added, followed by tetraphenyl pyrophosphate (0·518 g., 1 mol.; Corby, Kenner, and Todd, *loc. cit.*) in methyl cyanide (3 c.c.). After 1 hour the solution was evaporated and the residue dissolved in dry benzene (10 c.c.). To this solution, containing the mixed anhydride (VII), benzyl alcohol (0·11 c.c., 1 mol.) and 2 : 6-lutidine (0·115 c.c., 1 mol.) were added and the whole was set aside overnight. The resulting solution was then treated as in method 1 above and yielded dibenzyl aminophosphonate, m. p. and mixed m. p. 101—103° (0·125 g., 46%). When the amount of tertiary base used in the initial reaction with monobenzyl phosphite was increased to 2 mols. the yield of dibenzyl aminophosphonate fell to 26%.

Attempted Preparation of Dibenzyl Pyrophosphite (VIII).—Monobenzyl phosphite (1·54 g., 2 mols.) and diphenyl chlorophosphonate (0·93 c.c., 1 mol.) were dissolved in dry benzene (20 c.c.), and triethylamine (1·26 c.c., 2 mols.) was added gradually. After 6 hours triethylamine hydrochloride was filtered off and the liquors were washed with water (4 × 10 c.c.) before division into two equal parts.

(*a*) Evaporation of the solvent after drying (Na_2SO_4) gave an initially neutral oil (0·38 g.), which became strongly acid overnight.

(*b*) After washing with sodium hydrogen carbonate solution (2 × 15 c.c.), drying (Na_2SO_4), and evaporation there remained an oil (0·13 g.), which was neutral and did not develop acidity. This was identified as dibenzyl phosphite by conversion in 75% yield by means of *cyclo*hexylamine and carbon tetrachloride into dibenzyl *cyclo*hexylaminophosphonate, m. p. 79—81°, and by elementary analysis (Found: C, 63·6; H, 5·5; P, 11·9. Calc. for $C_{14}H_{15}O_3P$: C, 64·2; H, 5·7; P, 11·9%).

Inspection of paper chromatograms failed to reveal any reaction of either of the oils described in (*a*) and (*b*) above with 2′ : 3′-*iso*propylidene uridine in presence of 2 : 6-lutidine.

Dibenzyl p-*Bromobenzylaminophosphonate*.—This compound, required as a reference substance, was prepared by adding *p*-bromobenzylamine (1·1 g.; cf. Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3738) to a solution of dibenzyl phosphite (0·77 g.) in carbon tetrachloride (15 c.c.). Heat was evolved on mixing and after 1½ hours the mixture was heated to boiling and filtered hot, and the filtrate evaporated. The residue was recrystallised from light petroleum (b. p. 60—80°), giving *dibenzyl* p-*bromobenzylaminophosphonate* (1·2 g.) as fine colourless needles, m. p. 98—100° (Found: C, 56·6; H, 4·3; N, 3·2. $C_{21}H_{21}O_3NBrP$ requires C, 56·5; H, 4·7; N, 3·1%).

Benzyl p-*Nitrobenzyl Phosphite*.—Crude *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride (VII) (prepared from 1·76 g., 2 mols., of monobenzyl phosphite by method 1 above), dissolved in benzene (20 c.c.)–methyl cyanide (10 c.c.), was treated with *p*-nitrobenzyl alcohol (0·8 g., 1 mol.) and 2 : 6-lutidine (1·17 c.c., 2 mols.) at room temperature. After 45 minutes the mixture was evaporated and the residue dissolved in chloroform (30 c.c.). The solution was washed successively with water, saturated aqueous sodium hydrogen carbonate, saturated aqueous potassium hydrogen sulphate, and water, dried (Na_2SO_4), and evaporated, giving crude benzyl *p*-nitrobenzyl phosphite (1·43 g.) as a thick yellowish oil with an odour very similar to that of dibenzyl phosphite. Since it decomposed on attempted distillation it was not analysed but its identity was demonstrated as follows. (*a*) One half of the above product was dissolved in benzene (7 c.c.) and methyl cyanide (3 c.c.), and *N*-chlorosuccinimide (0·31 g.) added. After 2 hours excess of aqueous sodium hydrogen carbonate was added to the chlorophosphonate solution produced, and the whole stirred vigorously for 8 hours, then left overnight. The mixture was extracted with chloroform (10 c.c.), and the aqueous layer was

acidified and extracted with chloroform (3 × 20 c.c.). The chloroform extract was dried (Na_2SO_4) and evaporated, giving a pale yellow oil which gradually solidified. Recrystallised from chloroform–light petroleum (b. p. 60—80°), *benzyl* p-*nitrobenzyl hydrogen phosphate* was obtained as colourless needles (54%), m. p. 108—110° (Found: C, 52·0; H, 4·6; N, 4·6. $C_{14}H_{14}O_6NP$ requires C, 52·1; H, 4·3; N, 4·3%).

(*b*) The other half of the crude phosphite was treated as above with *N*-chlorosuccinimide and the product allowed to react with *cyclo*hexylamine (0·57 c.c., 2 mols.). Worked up in the usual way the reaction mixture gave *benzyl* p-*nitrobenzyl* cyclo*hexylaminophosphonate*, which crystallised from light petroleum (b. p. 60—80°) as colourless needles, m. p. 90—92° (Found: C, 59·5; H, 5·9; N, 7·1. $C_{20}H_{25}O_5N_2P$ requires C, 59·5; H, 6·2; N, 7·0%).

2′ : 3′-iso*Propylidene Uridine-5′ Benzyl Phosphite*.—*O*-Benzylphosphorous *OO*-diphenylphosphoric anhydride (VII) (prepared from 0·618 g., 2 mols., of monobenzyl phosphite by method 1 above and evaporation of solvent in the frozen state) was mixed with a solution of 2′ : 3′-*iso*propylidene uridine (0·52 g., 1 mol.; dried at 70°/0·1 mm. for 12 hours over phosphoric oxide) and 2 : 6-lutidine (0·42 c.c., 2 mols.) in methyl cyanide (25 c.c.), and the mixture was set aside for 3 hours. Solvent was removed by evaporation, the residue taken up in chloroform (25 c.c.), and the solution washed with water, saturated aqueous sodium hydrogen carbonate, potassium hydrogen sulphate, and again water, dried (Na_2SO_4), and evaporated; the crude phosphite so obtained (0·68 g.) was an almost colourless resin. On chromatography on Whatman No. 1 paper in *n*-butanol saturated with water, this showed a single spot absorbing ultra-violet radiation, containing phosphorus, and having R_P 0·8. A second minor spot contained phosphorus, but was not detected by ultra-violet light, and had the same R_P value, 0·9, as dibenzyl phosphite.

2′ : 3′-iso*Propylidene Uridine-5′ Benzyl* p-*Bromobenzylaminophosphonate*.—The phosphite prepared in the preceding experiment was dissolved in carbon tetrachloride containing 5% of methyl cyanide. On addition of *p*-bromobenzylamine (2 mols.), heat was evolved and *p*-bromobenzylamine hydrochloride separated immediately. After 3 hours the solution was filtered, washed with water, dried (Na_2SO_4), and evaporated. The p-*bromobenzylaminophosphonate* remained as a stable glass, containing bromine and having R_P 0·91 on Whatman No. 1 paper in *n*-butanol saturated with water (Found: C, 49·9; H, 4·5; N, 6·6; P, 5·3. $C_{26}H_{29}O_8N_3BrP$ requires C, 50·1; H, 4·7; N, 6·8; P, 5·0%).

2′ : 3′-iso*Propylidene Uridine-5′ Benzyl Hydrogen Phosphate*.—*N*-Chlorosuccinimide (0·335 g., 1 mol.; Tscherniac, *Ber.*, 1901, **34**, 4213) was added to a solution of 2′ : 3′-*iso*propylidene uridine-5′ benzyl phosphite (1·02 g., 1 mol.) in methyl cyanide (25 c.c.). After 2 hours an equal volume of a saturated aqueous solution of sodium hydrogen carbonate was added and the mixture stirred vigorously during 6 hours and then kept overnight. Methyl cyanide was distilled under reduced pressure from the liquors, which were acidified (Congo-red) with hydrochloric acid and extracted with chloroform (5 × 10 c.c.). Evaporation of the dried (Na_2SO_4) extracts left a hygroscopic glass, which was transformed into a colourless amorphous solid (0·87 g., 83% from 2′ : 3′-*iso*propylidene uridine) by pouring a concentrated chloroform solution into a large volume of dry ether. Like the 2′ : 3′-*iso*propylidene uridine-5′ benzyl hydrogen phosphate prepared by Mr. S. M. H. Christie, this had R_P 0·75 in *n*-butanol (5 volumes)–water (3 volumes)–acetic acid (1 volume) on Whatman No. 4 paper.

Uridine-5′ Benzyl Hydrogen Phosphate.—The foregoing *iso*propylidene derivative (0·100 g.) was kept during 15 hours with a 5% solution (1 c.c.) of hydrogen chloride in methanol. When the mixture was poured into dry ether (50 c.c.) turbidity developed and small rosettes of crystals (0·031 g.) were deposited. The *uridine-5′ benzyl hydrogen phosphate* had m. p. 129—132°, R_P 0·61 in *n*-butanol (5 volumes)–water (3 volumes)–acetic acid (2 volumes), and consumed 0·94 mol. of periodate ion per mol. during 24 hours at room temperature (Found: C, 46·5; H, 4·7; N, 6·8; P, 7·5. $C_{16}H_{19}O_9N_2P$ requires C, 46·4; H, 4·6; N, 6·8; P, 7·5%).

2′ : 3′-iso*Propylidene Adenosine-5′ Benzyl Phosphite*.—A solution of *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride (2 mols.) in benzene (30 c.c.) was prepared from monobenzyl phosphite (2·01 g.), diphenyl chlorophosphonate (2·42 c.c.), and triethylamine (1·65 c.c.). To this was added directly 2′ : 3′-*iso*propylidene adenosine (1·85 g., 1 mol.; dried during 12 hours at 90—100°/0·1 mm.), 2 : 6-lutidine (1·3 c.c., 2 mols.), and methyl cyanide (3 c.c.). When shaken at room temperature the mixture became homogeneous in about 10 minutes. After a further 20 minutes the solvents were evaporated and the residual oil was taken up in chloroform (30 c.c.) and washed twice with an equal volume of water, twice with 30 c.c. portions of saturated potassium hydrogen sulphate solution, and once with saturated sodium hydrogen carbonate solution. Evaporation of the dried (Na_2SO_4) solvent left the product (2·36 g.) as a stiff gum,

the main component of which had R_P 0·77 in *n*-butanol saturated with water on Whatman No. 1 paper and had an ultra-violet absorption maximum at 260 mμ. The minor component resembled dibenzyl phosphite and had R_P 0·9. The gum was taken up in dry benzene (15 c.c.) and poured into dry *cyclo*hexane (200 c.c.). The pure *phosphite* was separated by decantation as a heavy amorphous solid (1·9 g., 68%) (Found, in material dried at room temperature: C, 51·0; H, 5·2; N, 14·8; P, 6·7. $C_{20}H_{24}O_6N_5P,\frac{1}{2}H_2O$ requires C, 51·1; H, 5·3; N, 14·9; P, 6·6%).

2′ : 3′-iso*Propylidene Adenosine-5′ Benzyl* p-*Bromobenzylaminophosphonate*.—*p*-Bromobenzylamine (0·635 g., 2·5 mols.) was added to a solution of 2′ : 3′-*iso*propylidene adenosine-5′ benzyl phosphite (0·64 g., 1 mol.) in carbon tetrachloride (6 c.c.). The *p*-bromobenzylamine hydrochloride, which was rapidly precipitated, was removed by filtration after 2 hours and the filtrate was evaporated. The residual gum was dissolved in chloroform, which was washed with water, dilute hydrochloric acid, and saturated sodium hydrogen carbonate solution before drying (Na_2SO_4). The pale yellow stable glass (0·69 g.) obtained on evaporation was converted into a white amorphous *product* (0·505 g., 46% from 2′ : 3′-*iso*propylidene adenosine) by pouring a solution in chloroform (1 c.c.) into ether (50 c.c.) and then pouring a solution of the precipitated solid in benzene (1 c.c.) into *cyclo*hexane (50 c.c.) (Found: C, 50·3; H, 5·2; N, 12·9; P, 5·2. $C_{27}H_{30}O_6N_6BrP$ requires C, 50·3; H, 4·7; N, 13·0; P, 4·8%).

2′ : 3′-iso*Propylidene Adenosine-5′ Benzyl Hydrogen Phosphate*.—This was prepared from 2′ : 3′-*iso*propylidene adenosine-5′ benzyl phosphite in the same way as the uridine analogue as an amorphous solid (54% from 2′ : 3′-*iso*propylidene adenosine), having R_P 0·64 in *n*-butanol (4 volumes)–water (5 volumes)–acetic acid (1 volume) on Whatman No. 4 paper like an authentic specimen prepared by Mr. S. M. H. Christie from 2′ : 3′-*iso*propylidene adenosine-5′ dibenzyl phosphate (Baddiley and Todd, *J.*, 1947, 648).

Adenosine-5′ Benzyl Hydrogen Phosphate.—A solution of the *iso*propylidene derivative (0·14 g.) from the preceding preparation in ethanol (3 c.c.) was boiled during 1 hour with 0·02N-sulphuric acid (10 c.c.). When the solution cooled, adenosine-5′ benzyl hydrogen phosphate (0·08 g.) separated, having m. p. 228—230° alone or mixed with an authentic sample (Baddiley and Todd, *loc. cit.*).

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705. *Nucleotides. Part XVII.* N-Chloroamides as Reagents for the Chlorination of Diesters of Phosphorous Acid. A New Synthesis of Uridine-5′ Pyrophosphate.*

By G. W. KENNER, A. R. TODD, and F. J. WEYMOUTH.

N-Chlorosuccinimide and *N* : 2 : 4-trichloroacetanilide are shown to be satisfactory reagents for the preparation of dibenzyl and dialkyl chlorophosphonates from dibenzyl and dialkyl phosphites. 2′ : 3′-*iso*Propylidene-uridine-5′ benzyl phosphite has been chlorinated with *N*-chlorosuccinimide and from the product, by reaction with triethylammonium dibenzyl hydrogen phosphate and subsequent removal of protecting groups, uridine-5′ pyrophosphate has been synthesised. The pyrophosphate isolated as its barium salt has been shown to be identical with the major component of " barium uridine diphosphate " obtained from natural sources by direct comparison on paper chromatograms using several different solvent systems.

AMONG the theoretically possible methods for the synthesis of polynucleotides and nucleotide coenzymes which can be represented by the formulæ RO·PO(OH)·OR′ and RO·PO(OH)–O–PO(OH)·OR′ respectively, in which at least one of the groups R and R′ is a purine or pyrimidine nucleoside residue, the most obvious are those which employ nucleoside benzyl chlorophosphonates as intermediates. From the latter compounds the

* Part XVI, preceding paper.

polynucleotides or nucleotide coenzymes might be synthesised by well-established methods of phosphate and pyrophosphate preparation developed over a period of years in this laboratory. It was with this end in view that a study of methods for preparing nucleoside benzyl phosphites was undertaken; the development of a successful method employing mixed anhydrides of phosphorous and phosphoric acid derivatives has been reported in Part XVI.* Concurrently it was necessary to seek methods for the conversion of secondary phosphites into chlorophosphonates under conditions which would be applicable to the nucleoside benzyl phosphites. The present paper describes work leading to the discovery of such a method and the practical application of a nucleoside benzyl chlorophosphonate in the synthesis of uridine-5′ pyrophosphate.

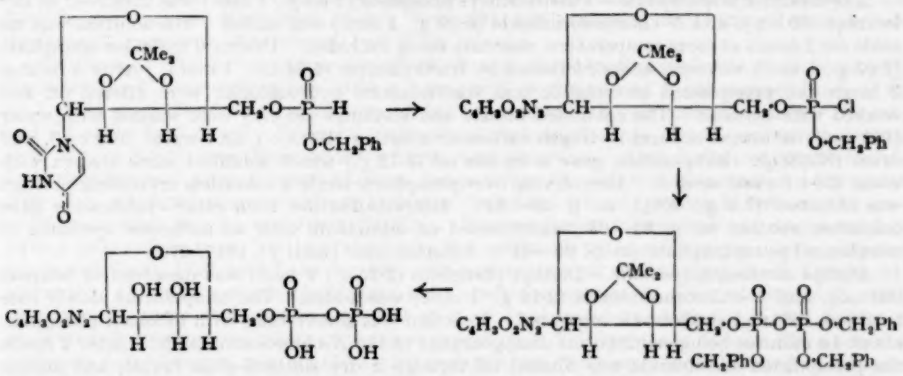
Dialkyl chlorophosphonates were first prepared from dialkyl phosphites by direct action of chlorine at room temperature, the hydrogen chloride evolved being removed by blowing air through the reaction mixture or by treatment with lead carbonate (McCombie, Saunders, and Stacey, *J.*, **1945**, 380). The same procedure was used for preparing the less stable dibenzyl chlorophosphonate (Atherton, Openshaw, and Todd, *J.*, **1945**, 382), although here it was necessary to work at a low temperature and to use an inert diluent. A somewhat milder reagent was later found in sulphuryl chloride which chlorinates dibenzyl phosphite readily at room temperature (Atherton, Howard, and Todd, *J.*, **1948**, 1106). Neither of these methods seemed suitable for our purposes, however, since large amounts of hydrogen chloride are produced in each and nucleoside benzyl phosphites are extremely labile to acids (Corby, Kenner, and Todd, Part XVI). The reaction between dialkyl phosphites and carbon tetrachloride in presence of bases (Atherton, Openshaw, and Todd, *J.*, **1945**, 660; Atherton and Todd, *J.*, **1947**, 674) yields dialkyl chlorophosphonates as initial products and Steinberg (*J. Org. Chem.*, **1950**, **15**, 637) has adapted this method to their preparation and isolation by allowing simple dialkyl phosphites to react with carbon tetrachloride in presence of only a small amount of a tertiary base. When applied to 2′ : 3′-*iso*propylidene uridine-5′ benzyl phosphite (Part XVI, *loc. cit.*), this procedure was disappointing owing to extensive side reactions (cf. Atherton, Openshaw, and Todd, *loc. cit.*).

Some years ago Dr. F. R. Atherton in this laboratory observed that when a solution of dibenzyl phosphite in an inert solvent was treated with *N*-bromosuccinimide and then with an amine good yields of the corresponding dibenzyl aminophosphonate were obtained, clearly as a result of the formation of dibenzyl bromophosphonate in the initial reaction. The greater instability of bromophosphonates compared with chlorophosphonates, and the readiness with which *N*-bromosuccinimide attacks pyrimidine nucleosides (uridine being brominated readily at room temperature), made this reagent unattractive and attention was directed to the less reactive *N*-chloroamides, a number of which have been examined by Ziegler (*Annalen*, **1942**, **551**, 80) as potential chlorinating agents in other fields. For convenience in use a stable crystalline reagent was desirable and *N*-chlorosuccinimide (Tscherniac, *Ber.*, 1901, **34**, 4213) and *N* : 2 : 4-trichloroacetanilide (Chattaway and Orton, *J.*, 1899, **75**, 1046) were chosen for study. In the absence of diluent both compounds reacted violently with dibenzyl phosphite, considerable heat being evolved, but in suitable inert solvents (*e.g.*, carbon tetrachloride, benzene, chloroform, ether or methyl cyanide) reaction proceeded smoothly with little rise in temperature. When using *N*-chlorosuccinimide it was found desirable to use about 20 volumes of solvent and the progress of the reaction could be followed by the separation of fine crystals of succinimide which replaced the denser *N*-chlorosuccinimide. With dibenzyl phosphite reaction was complete in about five minutes although in practice a longer reaction time was allowed; the yield of chlorophosphonate, determined by the usual assay methods, was almost quantitative. With diethyl phosphite the reaction was slower, but could be accelerated by halving the volume of solvent used, whereupon the mixture warmed spontaneously to about 50°. When *N* : 2 : 4-trichloroacetanilide was used as chlorinating agent more concentrated solutions were required (5 vols. of solvent) and in ether or benzene the 2 : 4-dichloroacetanilide produced separated quantitatively during the reaction. Although less reactive than *N*-chlorosuccinimide, *N* : 2 : 4-trichloroacetanilide may be a valuable reagent in the preparation of water-soluble phosphates or pyrophosphates from phosphites, since both

it and the 2 : 4-dichloroacetanilide produced from it are virtually insoluble in water and can thus be readily separated from the desired reaction products. The application of *N*-chloroamides in the preparation of a number of model substances from diesters of phosphorous acid is described in the Experimental section.

When applied to nucleoside benzyl phosphites the chlorination method using *N*-chlorosuccinimide gave excellent results, very little in the way of undesirable by-products being obtained (Part XVI, *loc. cit.*). *N*-Chlorosuccinimide does attack some nucleosides slowly, however, and the use of excess of chlorinating agent for prolonged periods is inadvisable. When a solution of 2′ : 3′-*iso*propylidene uridine in methyl cyanide was kept at room temperature for 7 days with *N*-chlorosuccinimide (1·5 mols.) or for 2 days with the same reagent in presence of triethylamine, a considerable amount of a new substance, presumably 2′ : 3′-*iso*propylidene 5-chlorouridine, was produced.

In Part XVI of this series (*loc. cit.*) examples were given of the synthesis of some simple



nucleotides *via* the *iso*propylidene nucleoside benzyl phosphites. As a further development of the use of these compounds it was desirable to synthesise a nucleoside pyrophosphate. As an example uridine-5′ pyrophosphate (uridine diphosphate, UDP) was selected in view of its importance as a breakdown product of the coenzyme uridine-diphosphate-glucose (UDPG) concerned in the conversion of galactose-1 phosphate into glucose-1 phosphate (Caputto, Leloir, Cardini, and Paladini, *J. Biol. Chem.*, 1950, **184**, 333). Moreover the original synthesis of this compound (Part XV; Anand, Clark, Hall, and Todd, *J.*, 1952, 3665), although not very convenient for preparation of the pyrophosphate in quantity, had provided the necessary data which would permit ready identification of intermediate and final products by paper-chromatographic methods. Crude 2′ : 3′-*iso*propylidene uridine-5′ benzyl phosphite prepared by a slight modification of the previous procedure (Part XVI, *loc. cit.*) was treated with *N*-chlorosuccinimide, and the product brought into reaction with triethylammonium dibenzyl phosphate. The resinous 2′ : 3′-*iso*propylidene uridine-5′ tribenzyl pyrophosphate so obtained was treated with lithium chloride in 2-ethoxyethanol to effect partial debenzylation. The product, which appeared to consist mainly of the lithium salt of 2′ : 3′-*iso*propylidene uridine-5′ benzyl pyrophosphate contaminated with lithium uridine-5′ benzyl pyrophosphate and some non-nucleosidic impurities derived from the original phosphite preparation, was hydrogenated to remove the remaining benzyl group (cf. Anand, Clark, Hall, and Todd, *loc. cit.*), hydrolysed with acid to remove the *iso*propylidene residue, and converted into its barium salt. Removal of barium phosphate and barium uridine-5′ phosphate from this material by re-precipitation yielded the pure barium uridine-5′ pyrophosphate, from which lithium uridine-5′ pyrophosphate was also prepared. The purified barium salt was shown to be identical with the synthetic product described by Anand *et al.* (*loc. cit.*) and with the main component of a sample of " barium uridine diphosphate " prepared from natural UDPG and kindly supplied by Dr. Leloir. The new synthesis was relatively efficient, for the purified barium uridine-5′ pyrophosphate was obtained in 25% overall yield from uridine.

Experimental

M. p.s are corrected.

Dibenzyl cyclo*Hexylaminophosphonate*.—Pure dibenzyl phosphite (1·3 g., 1 mol.) was dissolved in dry benzene (20 c.c.), and *N*-chlorosuccinimide (0·67 g., 1 mol.; Tscherniac, *loc. cit.*) was added. The solution became warm and succinimide separated rapidly. After 2 hours at room temperature the succinimide was filtered off through a dry sintered-glass funnel, and *cyclo*hexylamine (1·28 c.c., 2·1 mols.) was added to the filtrate. The solution was set aside for a further hour, *cyclo*hexylamine hydrochloride filtered off (0·61 g., 91%), and the filtrate washed with water (50 c.c.), saturated sodium hydrogen sulphate (50 c.c.) solution, and water (50 c.c.). The solution was dried and evaporated, giving a crystalline mass of dibenzyl *cyclo*hexylaminophosphonate (1·64 g.; m. p. 69—75°). Recrystallisation from *n*-hexane gave fine colourless needles (1·42 g., 80%), m. p. 77—79°, undepressed on admixture with an authentic specimen (m. p. 79—80°; Atherton, Openshaw, and Todd, *loc. cit.*).

Tetrabenzyl Pyrophosphate.—Pure dibenzyl phosphite (1·95 g., 1 mol.) was dissolved in dry benzene (30 c.c.), and *N*-chlorosuccinimide (0·99 g., 1 mol.) was added. The solution was set aside for 2 hours at room temperature, moisture being excluded. Dibenzyl hydrogen phosphate (2·07 g., 1 mol.) was next added, followed by triethylamine (1·04 c.c., 1 mol.). After a further 2 hours the precipitated succinimide and triethylamine hydrochloride were filtered off and washed with benzene. The combined filtrate and washings (50 c.c.) were washed with water (100 c.c.), saturated sodium hydrogen carbonate solution (100 c.c.), and water (100 c.c.), and dried (Na_2SO_4). Evaporation gave a mobile oil (3·72 g.) which solidified when shaken with water (20 c.c.) and seeded. After drying over phosphoric oxide a colourless crystalline product was obtained (3·6 g., 90%), m. p. 59—62°. Recrystallisation from ether–*cyclo*hexane gave colourless needles, m. p. 61—63°, undepressed on admixture with an authentic specimen of tetrabenzyl pyrophosphate (m. p. 60—61°; Atherton and Todd, *J.*, 1947, 674).

Diethyl Anilinophosphonate.—Diethyl phosphite (2·25 g., 1 mol.) was dissolved in benzene (20 c.c.), and *N*-chlorosuccinimide (2·18 g., 1 mol.) was added. The temperature slowly rose to about 50°, and succinimide separated. Reaction was slower than with dibenzyl phosphite, about 10 minutes being required for disappearance of the *N*-chlorosuccinimide. After 2 hours the precipitated succinimide was filtered off through a dry sintered-glass funnel, and aniline (3·13 c.c., 2·1 mols.) was added to the filtrate. Aniline hydrochloride separated rapidly and after a further 2 hours it was filtered off (1·8 g., 86%) and washed with benzene. The benzene filtrate and washings (50 c.c.) were washed with water (30 c.c.), N-hydrochloric acid (30 c.c.), saturated sodium hydrogen carbonate solution (30 c.c.), and water (30 c.c.), and dried (Na_2SO_4). Evaporation of the filtered solution gave a crystalline residue (3·27 g., 87%), m. p. 90—94°, which, recrystallised from aqueous ethanol, gave fine needles, m. p. 95—96°, undepressed on admixture with an authentic specimen of diethyl anilinophosphonate (m. p. 96·5°; McCombie, Saunders, and Stacey, *loc. cit.*).

Dibenzyl Hydrogen Phosphate.—Dibenzyl phosphite (2·22 g., 1 mol.) was dissolved in benzene (10 c.c.), and *N* : 2 : 4-trichloroacetanilide (2·66 g., 1·3 mols.; Chattaway and Orton, *loc. cit.*) was added. Warming to about 40° initiated a vigorous reaction and 2 : 4-dichloroacetanilide crystallised rapidly. The solution was set aside at room temperature for 2 hours, and the 2 : 4-dichloroacetanilide (1·79 g.) was filtered off and washed with benzene. Water (6 c.c.) and 2 : 6-lutidine (20 c.c.) were added to the combined filtrate and washings, and the mixture was set aside for 3 days at room temperature. Removal of solvents under reduced pressure gave a brown oil which was diluted with water (50 c.c.) and neutralised (phenolphthalein) with aqueous sodium hydroxide. The solution was extracted with chloroform (2 × 40 c.c.) and acidified with hydrochloric acid, producing a heavy oily emulsion which was extracted with chloroform (3 × 20 c.c.). The chloroform extract was dried (Na_2SO_4) and evaporated under reduced pressure, to give a pale yellow syrup which on being seeded with dibenzyl hydrogen phosphate set to a mass of crystals (2 g., 83%; m. p. 75—78°). Recrystallisation from chloroform–pentane gave pure dibenzyl hydrogen phosphate (1·83 g., 76%), m. p. 79—81°, undepressed on admixture with an authentic sample (m. p. 78—79°; Lossen and Köhler, *Annalen*, 1891, **262**, 209).

2′ : 3′-iso*Propylidene Uridine-5′ Benzyl Phosphite*.—A solution of ammonium monobenzyl phosphite (3·5 g.; Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815) in water (30 c.c.) was acidified with hydrochloric acid (10 c.c.; 3N) and extracted rapidly with chloroform (2 × 25 c.c.). The chloroform extract was dried (Na_2SO_4) and evaporated, to give monobenzyl hydrogen phosphite (2·43 g.) as a mobile oil which was dried overnight at 0·1 mm. over phosphoric oxide.

The monobenzyl phosphite was taken up in dry benzene (15 c.c.), and diphenyl chlorophosphonate (2·9 c.c., 1 mol.) was added. This solution was stirred magnetically while a solution of triethylamine (1·98 c.c., 1 mol.) in benzene (10 c.c.) was added dropwise during 10 minutes. After a further hour's stirring the resulting solution of *OO*-diphenylphosphoric *O*-benzylphosphorous anhydride was freed from triethylamine hydrochloride by filtration through a dry sintered-glass funnel and 2′ : 3′-*iso*propylidene uridine (2·02 g., 0·5 mol.; Levene, and Tipson, *J. Biol. Chem.*, 1934, **106**, 131), 2 : 6-lutidine (1·65 c.c., 1 mol.) and methyl cyanide (10 c.c.) were added. The 2′ : 3′-*iso*propylidene uridine dissolved rapidly. The solution was set aside at room temperature for 30 minutes, then evaporated, to yield a viscous syrup which was dissolved in chloroform (70 c.c.) and washed with water (70 c.c.), saturated aqueous sodium hydrogen carbonate (70 c.c.), saturated aqueous potassium hydrogen sulphate (70 c.c.), and water (2 × 70 c.c.). The dried chloroform solution was evaporated under reduced pressure, to give crude 2′ : 3′-*iso*propylidene uridine-5′ benzyl phosphite as a pale yellow syrup (3·34 g.).

Paper chromatography in *n*-propanol–water (85 : 15) showed the only component showing selective ultra-violet absorption to be the required phosphite (R_P 0·84), although spraying for phosphate (Hanes and Isherwood, *Nature*, 1949, **164**, 1107) revealed an additional phosphorus-containing component (R_P 0·90) (cf. Part XVI, *loc. cit.*).

Dilithium 2′ : 3′-iso*Propylidene Uridine-5′ Benzyl Pyrophosphate.*—Crude 2′ : 3′-*iso*propylidene uridine-5′ benzyl phosphite (3·34 g.; prepared as above) and *N*-chlorosuccinimide (1·02 g., 1 mol.) were dissolved in a mixture of dry benzene (50 c.c.) and methyl cyanide (10 c.c.) and set aside for 2 hours. Dibenzyl hydrogen phosphate (2·11 g., 1 mol.) and triethylamine (1·07 c.c., 1 mol.) were then added. There was immediate precipitation of triethylamine hydrochloride and after 2 hours at room temperature the solution was washed with water (100 c.c.), saturated aqueous sodium hydrogen carbonate (70 c.c.), hydrochloric acid (70 c.c.; N/50), and water (70 c.c.), and dried (Na_2SO_4). Evaporation of the solution at reduced pressure gave a pale yellow resin (4·41 g.), similar to the uridine-5′ tribenzyl pyrophosphate prepared by Anand, Clark, Hall, and Todd (*loc. cit.*). In each case paper chromatography in *n*-propanol–water (85 : 15) gave a single ultra-violet light absorbing spot of R_P 0·87, trailing to R_P 0·55, the lower R_P value corresponding to that of 2′ : 3′-*iso*propylidene uridine-5′ benzyl hydrogen phosphate formed by hydrolysis of the pyrophosphate. This resin was dissolved in a solution of freshly fused lithium chloride (1·28 g., 5 mols.) in dry 2-ethoxyethanol (25 c.c.) and heated at 100° for 2 hours to effect debenzylation. When cool, the solution was diluted with dry ethanol (20 c.c.) and poured into dry ether (80 c.c.), producing a flocculent white precipitate, which was centrifuged off, washed with dry acetone (2 × 80 c.c.) and dry ether (70 c.c.), and finally dried under reduced pressure at 60°; crude dilithium 2′ : 3′-*iso*propylidene uridine-5′ benzyl pyrophosphate (2·7 g.) was thus obtained as a hygroscopic white powder.

Paper chromatography of the product in butanol–acetic acid–water (50 : 10 : 40; upper layer) gave two main spots which absorbed ultra-violet light and contained phosphorus (R_P 0·17 and 0·40). When sprayed with neutral sodium periodate followed by Schiff's reagent (Buchanan, Dekker, and Long, *J.*, 1950, 3162), only the slower of these gave a positive reaction, indicating that the substance responsible for it contained a free α-glycol system, *i.e.*, that it had lost the 2′ : 3′-*iso*propylidene group. Very small amounts of slower-moving materials were also present, together with a considerable amount of faster-running phosphate impurity (R_P 0·55), possibly derived from the unknown contaminant of the uridine phosphite (see above). In 95% ethanol–ammonia (*d* 0·88) (2·5 : 1) the main products ran on paper chromatograms with R_P 0·57 and 0·64 respectively.

Barium Uridine-5′ Pyrophosphate.—The above crude lithium salt (1·6 g.) was dissolved in water (114 c.c.), acidified with hydrochloric acid (6 c.c. of N/10, giving a final concentration of N/200), and hydrogenated overnight at atmospheric pressure with a mixture of palladous oxide (Adams's catalyst, 0·2 g.) and palladised charcoal (0·2 g.; 10%). Catalyst was removed by filtration and washed thoroughly with water, and the combined filtrate and washings (190 c.c.) were treated with hydrochloric acid (6 c.c. of 3N, giving a final concentration of N/10) and set aside at room temperature overnight. After the solution had been brought to pH 7·1 with lithium hydroxide, barium bromide (1·31 g.) in water (5 c.c.) was added, the gelatinous precipitate of barium phosphate produced was filtered off through " Hyflo Supercel," and the filtrate evaporated to 80 c.c. under reduced pressure. A slight precipitate was centrifuged off and, after addition of more barium bromide (0·6 g.), the crude barium uridine-5′ pyrophosphate was precipitated by ethanol (2 vols). The gelatinous precipitate was centrifuged off, washed with acetone (100 c.c.) and ether (100 c.c.), and dried at 60° under reduced pressure, to give a fine white powder (1 g.). Paper chromatography in *iso*propyl alcohol–1% ammonium sulphate

solution (60 : 40) showed that this material contained, in addition to uridine-5′ pyrophosphate, small amounts of uridine-5′ phosphate (R_P 0·47) and of 2′ : 3′-*iso*propylidene uridine pyrophosphate (R_P 0·64). Optical-density measurements at 260 mμ on eluted spots showed the approximate composition to be uridine-5′ pyrophosphate 83%, uridine-5′ phosphate 7%, and 2′ : 3′-*iso*propylidene uridine-5′ pyrophosphate 10%.

The above crude barium salt (0·98 g.) was dissolved in 0·1N-hydrochloric acid (22 c.c.) and set aside at room temperature overnight. The filtered solution was then brought to pH 8 by addition of saturated aqueous barium hydroxide, and precipitation was completed by adding two volumes of ethanol. The precipitate was centrifuged off and washed with aqueous ethanol (45 c.c. of 70%), acetone (45 c.c.), and ether (45 c.c.). Drying at 60°/0·1 mm. gave a fine hygroscopic powder (0·96 g.) which rapidly reached constant weight on exposure to the atmosphere. Paper chromatography in *iso*propyl alcohol–1% aqueous ammonium sulphate (60 : 40) showed the 2′ : 3′-*iso*propylidene uridine-5′ pyrophosphate to have been completely removed, only a faint trace of uridine-5′ phosphate remaining. Phosphate analysis by Allen's method (*Biochem. J.*, 1940, **34**, 858), however, revealed 6% of the total phosphorus to be present as orthophosphate. To remove this the barium salt (1·71 g.) was dissolved in a minimum of 0·2N-hydrochloric acid and reprecipitated by ethanol (3 vols). The precipitate was collected, washed with acetone and ether, and dried at 60°/0·1 mm., giving monobarium uridine-5′ pyrophosphate as a fine white powder (1·08 g., 24% based on 2′ : 3′-*iso*propylidene uridine or 22% on uridine) (Found, in material exposed to the atmosphere for 24 hours: C, 17·6; H, 3·1; N, 4·4; P, 10·2%; total P/acid-labile P, 1·99 : 1. Calc. for $C_9H_{12}O_{12}N_2P_2Ba,4H_2O$: C, 17·7; H, 3·3; N, 4·6; P, 10·1. Calc. for $C_9H_{12}O_{12}N_2P_2Ba,3H_2O$: C, 18·2; H, 3·0; N, 4·7; P, 10·4%; total P/acid-labile P, 2 : 1). Concentration of the mother-liquors followed by precipitation with ethanol at pH 1 gave a further quantity of slightly less pure barium salt (0·21 g.). Inorganic phosphate amounted to less than 1% of the total phosphorus, and elution of the uridine-5′ phosphate and uridine-5′ pyrophosphate spots from a paper chromatogram (*iso*propyl alcohol–1% ammonium sulphate) with hydrochloric acid (N/100) and determination of the optical densities of the eluates at 260 mμ showed that the uridine-5′ phosphate present did not exceed 2% by weight. Ultra-violet absorption in N/100-HCl: max. 262—263 mμ (ε, 9070); min. 231 mμ (ε, 1910) (based on $C_9H_{12}O_{12}N_2P_2Ba,4H_2O$). The purified barium salt was identical with the barium uridine-5′ pyrophosphate of Anand, Clark, Hall, and Todd (*loc. cit.*) in paper-chromatographic behaviour and in infra-red spectrum.

Trilithium Uridine-5′ Pyrophosphate.—An aqueous solution of crude barium uridine-5′ pyrophosphate (0·1 g.) was passed slowly down an ion-exchange column (I.R.100 resin; 6 c.c.) saturated with lithium ions. To the eluate (15 c.c.) ethanol (40 c.c.) was added, producing a flocculent white precipitate which was centrifuged off, washed with ether, and dried at 60°/0·1 mm. *Trilithium uridine-5′ pyrophosphate* was thus obtained as a hygroscopic white powder (Found, in material dried over phosphoric oxide at 100°/1 mm.: C, 23·7; H, 3·2; N, 5·8. $C_9H_{11}O_{12}N_2P_2Li_3,2H_2O$ requires C, 23·6; H, 3·3; N, 6·1%). The acridine salt of uridine-5′ pyrophosphate proved to be too soluble in water to be useful for purification (solubility *ca.* 0·5 g./c.c.).

Identification of the Synthetic Barium Uridine-5′ Pyrophosphate with a Specimen of " Barium Uridine Diphosphate " isolated by Acid Hydrolysis of Natural UDPG.—The synthetic barium uridine-5′ pyrophosphate and the sample prepared from natural UDPG by Dr. L. Leloir were run side by side on paper chromatograms, using a number of solvent systems. Only acidic systems, or neutral systems containing ammonium sulphate, gave chromatograms free from trailing. In basic solvent systems the bulk of the barium salts failed to move from the starting line. The most satisfactory systems found were the four quoted below. No precautions were taken to standardise R_P values, which, particularly in the case of solvent *A*, varied with minor changes in the experimental conditions.

Substance	R_P in solvent system			
	A	*B*	*C*	*D*
Natural barium uridine diphosphate:				
(*a*) main component	0·47	0·43	0·14	0·24
(*b*) minor component (uridine-5′ phosphate)	0·64	0·59	0·25	0·44
Synthetic barium uridine-5′ pyrophosphate	0·47	0·43	0·16	0·25
Ammonium uridine-5′ phosphate	0·64	0·60	0·28	0·45

Solvent systems: *A*, *iso*propyl alcohol (60)–1% ammonium sulphate solution (40); *B*, *n*-propanol (45)–1% ammonium sulphate solution (35)–acetic acid (20); *C*, *n*-butanol (50)–acetic acid (20)–water (30); *D*, methanol (80)–98% formic acid (10)–1% ammonium sulphate solution (10). All solvent systems containing ammonium sulphate were run on Whatman No. 1 paper previously soaked in 1% ammonium sulphate solution and dried.

The relative molecular proportion of uridine-5′ pyrophosphate and uridine-5′ phosphate in the sample of " barium uridine diphosphate " of natural origin was found to be 9 : 1 by eluting the spots from a paper chromatogram (solvent system *A* above) with N/100-hydrochloric acid and measuring the relative optical densities (1·50 and 0·166 respectively) at 260 mμ with a Beckmann quartz spectrophotometer; elution of the spots was practically quantitative. Determination of orthophosphate by Allen's method (*loc. cit.*) showed that the same sample of " barium uridine diphosphate " contained 5·2% by weight of orthophosphate, assumed to be present as $BaHPO_4$.

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706. *Nucleotides. Part XVIII.* The Synthesis and Properties of Adenosine-5′ Uridine-5′ Phosphate.*

By D. T. ELMORE and A. R. TODD.

Adenosine-5′ uridine-5′ phosphate (I) has been synthesised by the interaction of silver 2′ : 3′-*iso*propylidene adenosine-5′ benzyl phosphate and 2′ : 3′-*iso*-propylidene 5′-iodo-5′-deoxyuridine in boiling toluene. It is stable towards alkali and ribonuclease. These findings are discussed in relation to current theories of ribonucleic acid structure and ribonuclease action. Rapid degradation to adenosine and uridine is brought about by crude Russell's viper venom.

INVESTIGATIONS of the structure of nucleic acids have been largely concerned in recent years with the establishment of the nature of the internucleotide linkage and the determination of the ratio and sequence of purine and pyrimidine bases. The methods employed have broadly followed two paths. On the one hand, chemical and enzymic hydrolysates have been examined by the techniques of ion-exchange chromatography (Carter and Cohn, *J. Amer. Chem. Soc.*, 1950, **72**, 2604; Cohn, *J. Cell. Comp. Physiol.*, 1951, **38**, Suppl. 1, 21; Koerner and Sinsheimer, *J. Amer. Chem. Soc.*, 1952, **74**, 283), paper chromatography (Carter, *ibid.*, 1950, **72**, 1466; Chargaff, *Experientia*, 1950, **6**, 201), and electrophoresis (Gordon and Reichard, *Biochem. J.*, 1951, **48**, 569; Markham and Smith, *Nature*, 1951, **168**, 406; Smith and Markham, *Biochim. Biophys. Acta*, 1952, **8**, 350). The discovery of isomeric *a* and *b* ribonucleotides, the isolation of a number of di- and tri-nucleotides, and the rejection of the " tetranucleotide " theory of nucleic acid structure have resulted. On the other hand, synthetical work, which has been in progress in this laboratory for a number of years, has culminated in the elucidation of most of the structural features of the nucleotides. It seemed desirable to extend the latter investigations to include the synthesis by unequivocal methods of diribonucleoside phosphates and diribonucleotides in order to investigate the stability of the various possible phosphodiester linkages to hydrolysis by alkali and enzymes. In addition, the effect of the purine and pyrimidine moieties of the diribonucleoside phosphates and diribonucleotides on ribonuclease specificity might be determined.

The resistance to alkali of the phosphoryl groups of ribonucleotides (previously designated as 3′-phosphates) and ribose-5′ phosphate led Levene and Tipson (*J. Biol. Chem.*, 1935, **109**, 623) to postulate a $C_{(2')}$–$C_{(3')}$ internucleotide linkage which would undergo alkaline cleavage at $C_{(2')}$. Gulland and Smith (*J.*, 1947, 338; 1948, 1527) claimed to have synthesised uridine-2′ and cytidine-2′ phosphates and diuridine-2′ : 2″ phosphate (*J.*, 1948, 1532) in order to test this hypothesis. Michelson and Todd (*J.*, 1949, 2476) also attempted the synthesis of the 2′-phosphates of guanosine, adenosine, and cytidine. It was subsequently shown, however, that the synthetic route employed in all these cases afforded 5′-substituted nucleosides (Brown, Haynes, and Todd, *J.*, 1950, 408,

* Part XVII, preceding paper.

3299). Independent investigations had resulted meanwhile in the separation of each of the nucleotides from the alkaline hydrolysis of yeast ribonucleic acid into two isomers, neither of which corresponded with the known synthetic nucleoside-5′ phosphates (Carter and Cohn, *Fed. Proc.*, 1949, **8**, 190; Cohn, *J. Amer. Chem. Soc.*, 1950, **72**, 1471, 2811; Loring, Luthy, Bortner, and Levy, *ibid.*, p. 2811; Loring and Luthy, *ibid.*, 1951, **73**, 4215; Carter, *loc. cit.*). It is now generally accepted that the *a* and the *b* isomers are 2′- and 3′-phosphates though not necessarily respectively; the recent synthesis of *a* and *b* adenylic acids by direct phosphorylation of 5′-trityl adenosine (Brown and Todd, *J.*, 1952, 44) supports this view. Both *a* and *b* ribonucleotides are stable to alkali under conditions which cause hydrolysis of yeast ribonucleic acid to mononucleotides. Thus, although the $C_{(2')}$–$C_{(3')}$ linkage cannot be completely excluded on this ground, since both *a* and *b* nucleotides are formed by alkaline hydrolysis of ribonucleic acid, the original premises of Levene and Tipson are unsound.

In spite of the repeated failure to isolate nucleoside-5′ phosphates from alkaline hydrolysates of ribonucleic acids and their known stability to alkali, early enzymic experiments (Gulland and Jackson, *J.*, 1938, 1492) did, in fact, indicate the participation of $C_{(5')}$ in at least some of the internucleotide linkages. Incontrovertible proof was forthcoming when Cohn and Volkin (*Nature*, 1951, **167**, 483) separated by ion-exchange chromatography the 5′-phosphates of adenosine, guanosine, cytidine, and uridine from digests of ribonucleic acid treated successively with ribonuclease and intestinal phosphatase in presence of arsenate to inhibit phosphomonoesterase. Very recently, Cohn and Volkin (*Arch. Biochem.*, 1952, **35**, 465) have isolated diphosphates of cytidine and uridine which are believed to have phosphoryl groups at $C_{(3')}$ (or $C_{(2')}$) and $C_{(5')}$.

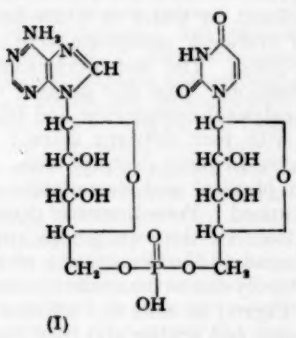
From the evidence cited above and considerable data relating to the interconversion of glycerol α- and β-phosphates and *a* and *b* ribonucleotides by acid, and the alkali-lability of glycerol α-(methyl hydrogen phosphate) and of esters of the *a* and *b* nucleotides, Brown and Todd (*J.*, 1952, 52) have advanced an explanation of the hydrolytic behaviour of ribonucleic acids. A $C_{(3')}$–$C_{(5')}$ (or $C_{(2')}$–$C_{(5')}$) internucleotide linkage is postulated for ribonucleic acids, and cleavage of the macromolecule by alkali is preceded by the formation of a cyclic triester involving the vicinal $C_{2'}$- (or $C_{3'}$-)hydroxyl group. Hydrolysis of the $C_{(5')}$–O–P linkage then occurs and the resulting nucleoside 2′ : 3′-cyclic phosphates (Brown, Magrath, and Todd, *J.*, 1952, 2708) ultimately afford mixtures of 2′- and 3′-phosphates. Taken alone, this mechanism of hydrolysis would permit $C_{(2')}$–$C_{(2')}$, $C_{(2')}$–$C_{(3')}$, $C_{(3')}$–$C_{(3')}$, $C_{(2')}$–$C_{(5')}$, and $C_{(3')}$–$C_{(5')}$, but would exclude $C_{(5')}$–$C_{(5')}$, as possible internucleotide linkages. Moreover, the concomitant formation of *a* and *b* ribonucleotides during hydrolysis is adequately explained without necessarily involving a $C_{(2')}$–$C_{(3')}$ linkage.

The mechanism of ribonuclease action is less clear. Markham and Smith (*loc. cit.*) believe that degradation of ribonucleic acids by ribonuclease simulates that by alkali with the important difference that $C_{(3')}$–$C_{(5')}$ (or $C_{(2')}$–$C_{(5')}$) internucleotide linkages are cleaved only if $C_{(3')}$ (or $C_{(2')}$) refers to a ribose residue bearing a pyrimidine base. Some confirmation of this qualification has been evinced from a study of the action of ribonuclease on cyclic nucleoside-2′ : 3′ phosphates (Brown, Dekker, and Todd, *J.*, 1952, 2715). Cyclic phosphates of uridine and cytidine are cleaved by ribonuclease to yield only the *b* nucleotide whereas cyclic adenosine-2′ : 3′ phosphate is unaffected by the enzyme (cf. Markham and Smith, *loc. cit.*). Recently, Allen (*Fed. Proc.*, 1951, **10**, 155), Becker and Allen (*J. Biol. Chem.*, 1952, **195**, 429), and Cavalieri, Kerr, and Angelos (*J. Amer. Chem. Soc.*, 1951, **73**, 2567) have observed that ribonuclease digests of ribonucleic acids show an increased uptake of periodate. On the other hand, Schmidt and his co-workers (*J. Biol. Chem.*, 1951, **192**, 715) obtained completely negative results in a similar investigation. Brown and Todd (*J.*, 1952, 52) have pointed out that, if the observations of Allen (*locc. cit.*) and Cavalieri, Kerr, and Angelos (*loc. cit.*) are valid, ribonuclease action must be more complex than indicated above, since an increased uptake of periodate by ribonuclease digests can arise only if some $C_{(3')}$–O–P (or $C_{(2')}$–O–P) linkages are severed as well as $C_{(5')}$–O–P linkages. In order to clarify this remarkable disparity, the action of ribonuclease on simple model substrates including diribonucleoside phosphates is under investigation in this laboratory.

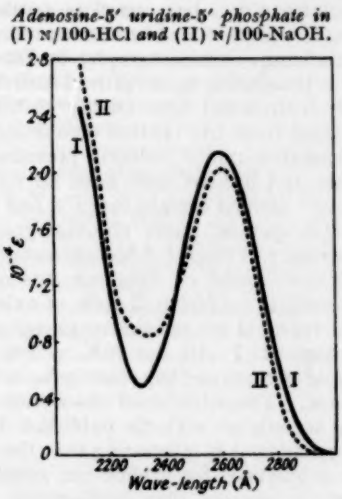
The only diribonucleoside phosphate so far synthesised is diuridine phosphate (Gulland

and Smith, *J.*, 1948, 1532), which, as mentioned above, is now known to possess a $C_{(5')}$–$C_{(5')}$ linkage. The synthetical route employed, which involved the reaction of 2 mols. of benzylidene uridine with 1 mol. of phenyl dichlorophosphinate, has several deficiencies. First, removal of the phenyl residue requires conditions which would almost certainly degrade a diribonucleoside phosphate containing any phosphodiester linkage except the type $C_{(5')}$–$C_{(5')}$. Secondly, reaction of phenyl dichlorophosphinate with dissimilar nucleosides would inevitably afford mixtures of diribonucleoside phosphates, thereby increasing the difficulty of isolating pure products. Finally, in the absence of a reagent which will block $C_{(3')}$ and $C_{(5')}$ (or $C_{(2')}$ and $C_{(5')}$) of the ribose moiety, unequivocal synthesis of diribonucleoside phosphates with ester linkages involving $C_{(2')}$ and/or $C_{(3')}$ is impossible.

The method which we have employed in the present work involves the heterogeneous reaction in anhydrous inert solvents of a silver salt of a suitably protected nucleotide with 2′ : 3′-*iso*propylidene 5′-iodo-5′-deoxyuridine. This method may be limited to the synthesis of diribonucleoside phosphates in which the $C_{(5')}$-position of uridine is esterified, since it has recently been demonstrated that attempts to prepare 5′-iodo-5′-deoxy-derivatives of adenosine and cytidine by the well-known Oldham–Rutherford method (*J. Amer. Chem. Soc.*, 1932, **54**, 366) lead to *cyclo*nucleoside salts by a novel intramolecular alkylation (Clark, Todd, and Zussman, *J.*, 1951, 2952). It is not known whether 5′-tosyl guanosine exhibits similar behaviour. Moreover, 2′-iodo-2′-deoxy- and 3′-iodo-3′-deoxy-ribonucleosides are as yet unknown and it is probable that the halogen substituent would, in any case, be too inert for these substances to be practicable intermediates for the synthesis of diribonucleoside phosphates by this route. Nevertheless, it seemed desirable to explore the potentialities of the reaction outlined, since by its use a limited number of unsymmetrical diribonucleoside phosphates might be made accessible.



(I)



This type of reaction has been utilised previously in the carbohydrate and nucleotide field. The Cori ester and its L-enantiomorph have been synthesised by the interaction of trisilver phosphate and the appropriate 2 : 3 : 4 : 6-tetra-acetyl α-bromoglucose in benzene (Cori, Colowick, and Cori, *J. Biol. Chem.*, 1937, **121**, 465; Wolfrom and Pletcher, *J. Amer. Chem. Soc.*, 1941, **63**, 1050; Potter, Sowden, Hassid, and Doudoroff, *ibid.*, 1948, **70**, 1751). Trisilver phosphate was also employed by Meagher and Hassid (*ibid.*, 1946, **68**, 2135) for the synthesis of maltose-1 and xylose-1 phosphates. The β-isomer of the Cori ester was surprisingly formed when silver dibenzyl phosphate was substituted for trisilver phosphate (Zervas, *Naturwiss.*, 1939, **27**, 317; Wolfrom, Smith, Pletcher, and Brown, *J. Amer.*

Chem. Soc., 1942, **64**, 23). Reithel (*ibid.*, 1945, **67**, 1056) obtained β-D-galactose-1 phosphate in an analogous fashion. In this department uridine-5′ phosphate and uridine-5′ pyrophosphate (UDP) have been synthesised conveniently and in good yield by the interaction of 2′ : 3′-*iso*propylidene 5′-iodo-5′-deoxyuridine in benzene with silver dibenzyl phosphate and silver tribenzyl pyrophosphate respectively (Anand, Clark, Hall, and Todd, *J.*, 1952, 3665).

In applying this method to the synthesis of adenosine-5′ uridine-5′ phosphate (I) several variations were investigated. Although some reaction occurred between the disilver salt of adenosine-5′ phosphate or silver adenosine-5′ benzyl phosphate and 2′ : 3′-*iso*propylidene 5′-iodo-5′-deoxyuridine in boiling toluene, best results were obtained when silver 2′ : 3′-*iso*propylidene adenosine-5′ benzyl phosphate was employed. Boiling benzene and dioxane were also tried as reaction media but were inferior to toluene. Isolation of the fully protected diribonucleoside phosphate has proved impossible. In consequence, *iso*propylidene and benzyl groups were removed by hydrolysis with dilute sulphuric acid, a method which proved useful during the synthesis of adenosine-5′ benzyl phosphate (Baddiley and Todd, *J.*, 1947, 648). In all cases reaction mixtures were examined by paper chromatography, but complete purification by this technique alone was not possible owing to the presence of a number of by-products which have not been further investigated. Ion-exchange chromatography on Dowex 2 resin in the formate cycle, with 0·08N-formic acid as the eluting agent, proved entirely satisfactory, since most of the impurities appeared to be neutral and were readily eluted from the column by water or 0·02N-formic acid. Fractions from the column containing adenosine-5′ uridine-5′ phosphate were combined, concentrated under reduced pressure, and freeze-dried. The free nucleotide and its barium and brucine salts have all resisted crystallisation. That our product was pure, however, seemed certain, since it had the correct analytical composition and travelled as a single spot on paper chromatograms irrigated with four different solvent systems; furthermore, it migrated homogeneously when subjected to paper electrophoresis.

Definite proof of structure was obtained from physical and degradative evidence. On periodate oxidation, 2 mols. of oxidant were consumed. Potentiometric titration with alkali revealed no secondary phosphoryl dissociation. Of the two groups titrating in the range pH 3—10, one ($pK_a = 3·8$) can be attributed to the dissociation of the NH_3^+ group of adenine and the other ($pK_a = 9·5$) is undoubtedly due to the enolic hydroxyl group of uracil. The ultra-violet absorption spectra (see Figure) in acid and alkaline solution are in accordance with the published data for adenosine and uridine and their derivatives. In particular, it is interesting that the shift of the minimum in alkaline solution is similar to that observed for uridine but smaller in magnitude. Russell's viper venom, which is known to possess phosphodiesterase and phosphomonoesterase activities (Hurst and Butler, *J. Biol Chem.*, 1951, **193**, 91), brought about complete hydrolysis within 2 hours to adenosine and uridine. The nucleosides were identified by paper chromatography and determined by cutting out the spots, elution, and measuring the optical density at the ultra-violet absorption maximum. A value of 0·98 was computed for the ratio, mols. of adenosine : mols. of uridine, in good agreement with the theoretical figure. Purified phosphodiesterase from Russell's viper venom (Hurst and Butler, *loc. cit.*) caused random fission of the phosphodiester to mononucleotides and nucleosides.

Adenosine-5′ uridine-5′ phosphate is stable to treatment with 0·5N-sodium hydroxide at 37° for 16 hours, conditions which effect complete hydrolysis of ribonucleic acids to mononucleotides. The absence of the $C_{(5')}$–$C_{(5')}$ internucleotide linkage in ribonucleic acids is thus proved, since such linkages if present would remain unbroken and products other than simple nucleotides would result. Moreover, ribonuclease has no action on adenosine-5′ uridine-5′ phosphate, a result which accords with current theories of ribonuclease specificity (Brown, Dekker, and Todd, *loc. cit.*, Markham and Smith, *loc. cit.*). Synthesis of further examples of diribonucleoside phosphates are under investigation. In particular, it is hoped to obtain compounds possessing a $C_{(3')}$–$C_{(5')}$ (or $C_{(2')}$–$C_{(5')}$) internucleotide linkage, since such compounds should undergo ready alkaline hydrolysis to a mixture of *a* and *b* adenylic acids and uridine, thus constituting a rigid test of Brown and Todd's theory (*loc. cit.*) regarding hydrolytic behaviour and structure of the ribonucleic acids.

Experimental

*Silver 2′ : 3′-iso**Propylidene Adenosine-5′ Benzyl Phosphate*** (first prepared in this Department by Dr. H. S. Mason).—2′ : 3′-*iso*Propylidene adenosine-5′ dibenzyl phosphate (3·0 g.), previously dried over phosphoric oxide in a high vacuum, was heated in freshly distilled 4-methylmorpholine (25 g.) for 1 hour in a stoppered flask at 100°. 4-Methylmorpholine was then removed under reduced pressure, the residue dissolved in water (100 c.c.), and the solution extracted with chloroform (3 × 100 c.c.). 2% Aqueous silver nitrate was added until precipitation of *silver 2′ : 3′-iso**propylidene adenosine-5′ benzyl phosphate*** was complete. The solid was centrifuged and washed by resuspension with distilled water until the supernatant liquid was colourless and the silver salt tended to become colloidal. It was then freeze-dried, with exclusion of light, to a fine white powder (3·0 g.) (Found : Ag, 21·3, 21·4; N, 11·4. $C_{20}H_{23}O_7N_5PAg$ requires Ag, 21·6; N, 11·9%).

Adenosine-5′ Uridine-5′ Phosphate.—Silver 2′ : 3′-*iso*propylidene adenosine-5′ benzyl phosphate (748 mg.) and 2′ : 3′-*iso*propylidene 5′-iodo-5′-deoxyuridine (505 mg., 1 mol.; Levene and Tipson, *J. Biol. Chem.*, 1934, **106**, 113) were suspended in dry toluene (100 c.c.) and heated under reflux for 8 hours with exclusion of light and moisture. Intimate contact of the reactants was maintained by placing several glass beads in the reaction flask and agitating by means of a stainless-steel paddle stirrer. After reaction the solution was filtered and the silver salts were washed thoroughly with warm ethanol. The combined filtrate and washings were evaporated under reduced pressure to small bulk, and the residue was evaporated twice with ethanol to remove toluene. The ethanolic solution (25 c.c.) was refluxed with N/50-sulphuric acid (80 c.c.) for 1½ hours. Sulphate was removed by the calculated amount of barium hydroxide solution. Barium sulphate was removed by filtration and washed thoroughly with hot water. The combined filtrate and washings were adjusted to pH 8·0 with aqueous ammonia and run on to a column (13·7 × 3·0 cm.) of Dowex 2 resin (250—500 mesh; formate cycle). Elution was carried out successively with 0·02N-, 0·05N-, and 0·08N-formic acid. The bulk of impurities were removed by the first two solvents, as revealed by paper chromatography of various fractions. *Adenosine-5′ uridine-5′ phosphate* was eluted by 0·08N-formic acid (optical density ratio, $D_{280}/D_{260} = 0{\cdot}30 \pm 0{\cdot}015$). Fractions having an optical density greater than 0·2 × maximum optical density were combined and concentrated under reduced pressure to small bulk and freeze-dried to a white hygroscopic fluffy solid (227 mg). The product was redissolved in a minimum of water and precipitated by addition of ethanol and ether, being then obtained as a white, amorphous, hygroscopic powder which decomposed at 180—200° without melting (Found, in material dried at 100°/0·1 mm. for 16 hours : C, 39·6; H, 3·8; P, 5·4, 5·9; N, 17·3. $C_{19}H_{24}O_{13}N_7P$ requires C, 39·8; H, 4·0; P, 5·4; N, 17·1%).

Adenosine-5′ uridine-5′ phosphate travelled as a single spot on acid-washed Whatman No. 1 paper (Hanes and Isherwood, *Nature*, 1949, **164**, 1107) in the following solvent systems : (1) *n*-butanol–acetic acid–water (40 : 10 : 50; the upper layer was used to irrigate the chromatogram; $R_P = 0{\cdot}08$) (Partridge, *Biochem. J.*, 1948, **42**, 238), (2) *n*-butanol–acetic acid–water (50 : 20 : 30); $R_P = 0{\cdot}26$, (3) *iso*propyl alcohol–ammonia (*d* 0·88)–water (70 : 10 : 20; $R_P = 0{\cdot}29$) and (4) 5% disodium hydrogen phosphate–*iso*amyl alcohol ($R_P = 0{\cdot}61$) (Carter, *loc. cit.*). The product migrated homogeneously when applied to Whatman No. 54 paper buffered at pH 7 with 0·1% ammonium acetate–ammonia solution and subjected to electrophoresis. Treatment with sodium metaperiodate (0·025M) overnight resulted in a consumption of 2·08 mol./mol. (mean of three determinations). Ultra-violet absorption : (1) In N/100-sulphuric acid, max. at 2590—2600 Å (ε 21,300), min. at 2310—2315 Å (ε 4860); (2) in N/100-sodium hydroxide, max. at 2600—2610 Å (ε, 20,300), min. at 2335—2340 Å (ε 8470). Potentiometric titration of adenosine-5′ uridine-5′ phosphate (14·9 mg.) in water (1 c.c.) with 0·105N-sodium hydroxide, with a glass electrode, demonstrated the absence of secondary phosphoryl dissociation and revealed the presence of two groups pK_a 3·8, 9·5 which are attributed to the dissociation of NH_3^+ of adenosine and enolic hydroxyl of uracil respectively.

Action of Alkali on Adenosine-5′ Uridine-5′ Phosphate.—Adenosine-5′ uridine-5′ phosphate (1·8 mg.) was dissolved in 0·5N-sodium hydroxide (0·2 c.c.) and kept at 37° for 16 hours. Paper chromatography, with *iso*propyl alcohol–ammonia (*d* 0·88)–water (70 : 10 : 20), showed that no hydrolysis had occurred.

Action of Ribonuclease on Adenosine-5′ Uridine-5′ Phosphate.—Adenosine-5′ uridine-5′ phosphate (1·9 mg.) was dissolved in water (0·1 c.c.) and a solution (0·6 mg./c.c.) of ribonuclease (0·1 c.c.) added. The pH was adjusted to 8·0 by dilute aqueous ammonia, and the digest kept

at 37° for 16 hours. Paper chromatography, with *iso*propyl alcohol–ammonia–water, revealed that no degradation had occurred.

Action of Russell's Viper Venom on Adenosine-5' Uridine-5' Phosphate.—Adenosine-5' uridine-5' phosphate (1 mg.) was dissolved in 0·25M-glycine–ammonia buffer (0·1 c.c.; pH 9·0) and treated with a solution of crude Russell's viper venom at 37° for 2 hours. Paper chromatography, with *n*-butanol–acetic acid–water (40 : 10 : 50), showed that hydrolysis to adenosine and uridine was complete. The spots were cut out and eluted with water, and the amounts of nucleoside determined by ultra-violet absorption measurements, giving a ratio, adenosine : uridine = 0·98. This experiment was repeated with the Russell's viper venom phosphodiesterase purified by paper chromatography (Hurst and Butler, *loc. cit.*). Hydrolysis of the diester linkage appeared to occur in a random fashion. Adenosine and uridine were identified by paper chromatography as before.

We thank Drs. R. Markham and J. D. Smith for a gift of Russell's viper venom and the purified phosphodiesterase therefrom. This work was carried out during the tenure by one of us (D. T. E.) of a Junior Beit Memorial Fellowship for Medical Research.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, April 30th,* 1952.]

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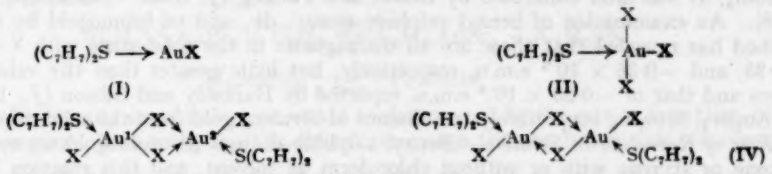
707. *The Nature of Benzyl Sulphide–Dibromo- and –Dichloro-gold.*

By F. H. BRAIN, (the late) C. S. GIBSON, J. A. J. JARVIS, R. F. PHILLIPS, H. M. POWELL, and A. TYABJI.

Measurement of molecular weight, electrical conductivity, and magnetic susceptibility has shown that the compound of empirical formula $(C_7H_7)_2S,AuBr_3$ cannot be formulated as a dimer, a salt, or a compound of bivalent gold, and *X*-ray investigation of the corresponding chloride has shown the presence in the crystal of separate molecules of benzyl sulphide–monochlorogold (I; X = Cl) and benzyl sulphide–trichlorogold (II; X = Cl) so arranged that a highly disordered structure results. From a comparison of the rates of reduction of $(C_7H_7)_2S,AuBr_3$ and benzyl sulphide–tribromogold in chloroform by styrene it is concluded that the former also exists in solution as an equimolecular mixture of the mono- and the tri-bromide (I and II; X = Br).

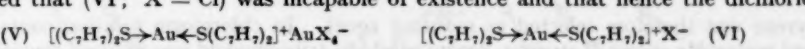
WHILST there is considerable evidence to show that gold, unlike the other metals of group IB, is unable to exert a valency of two and exists in its compounds only in the univalent (two-covalent) or tervalent (four-covalent) state, the literature contains references to a number of compounds which have been represented as derivatives of the bivalent metal. Such a one is that first isolated by Hermann (*Ber.*, 1905, **38**, 2813) by interaction of ethereal solutions of "auric chloride" and benzyl sulphide, which he formulated as $(C_7H_7)_2S,AuCl_2$ (hereafter referred to as benzyl sulphide–dichlorogold or the dichloride) though its molecular weight (604—608) in boiling chloroform was considerably in excess of the theoretical. Other purely inorganic examples were discussed by Sidgwick ("The Chemical Elements and Their Compounds," Oxford Univ. Press, 1950, p. 177) who considered that they must be complexes containing equal numbers of aurous and auric atoms, though experimental evidence of this has so far only been available in the case of the compounds $CsAuCl_3$, referred to below, and $Cs_2AgAuCl_6$. Unlike most of these compounds, that isolated by Hermann can be recrystallised and was described by him as separating from chloroform in "fiery orange silky needles." The same substance was obtained by Ray and Sen (*J. Indian Chem. Soc.*, 1930, **7**, 67) by mixing chloroform solutions containing equimolecular proportions of benzyl sulphide–monochlorogold (I; X = Cl) and benzyl sulphide–trichlorogold (II; X = Cl). This method of preparation and the fact that the substance reacted with potassium thiocyanate to give potassium aurithiocyanate, $KAu(SCN)_4$, together with (I; X = Cl), which is unaffected by this reagent. convinced them that it was a compound of (I) and (II) (X = Cl). However, their representation of it as $AuCl_3(C_6H_5{\cdot}CH_2)_2S,AuCl(C_6H_5{\cdot}CH_2)_2S$, though supported by an

observed molecular weight of 944 (theoretical 946) in benzene, did nothing to clarify the mode of compound formation. Such a compound could be formulated in two ways (III and IV; X = Cl. Cf. Gibson, Presidential Address, Section B, British Association, 1938) in which the two gold atoms are united by halogen bridges as in diethylbromogold (Burawoy, Gibson, Hampson, and Powell, *J.*, 1937, 1690). In (III) Au^1 is tervalent with an effective atomic number (E.A.N.) of 86 and Au^2 is univalent with E.A.N. 84, whilst



in (IV) both gold atoms are bivalent with E.A.N. 85, each therefore having one unpaired electron. It appears from the work of Dothie, Llewellyn, Wardlaw, and Welch (*J.*, 1939, 426) that the valencies of four-covalent aurous gold are coplanar and, if that is so, resonance would be possible in the bridge system of (III).

Smith (*J. Amer. Chem. Soc.*, 1922, **44**, 1769) prepared the analogous dibromide, di-iodide, and iodochloride and discussed the possibility that these and the dichloride might be salts (V; X = halogen) in which the cation contains a univalent and the anion a tervalent gold atom. However, failing to find any increase in the electrical conductivity of an alcoholic solution of (I; X = Cl) on progressive addition of benzyl sulphide, he concluded that (VI; X = Cl) was incapable of existence and that hence the dichloride



was not to be formulated as (V; X = Cl) which has the same cation as (VI). It has now been shown that salts of type (VI) can be prepared, providing X^- is an anion of low polarisability, by the interaction of benzyl sulphide–monobromogold (I; X = Br) and benzyl sulphide in an inert solvent with the appropriate solid silver salt. From the nitrate and the perchlorate (VI; X = NO_3^- and ClO_4^- respectively), which were isolated in this manner, one molecule of benzyl sulphide was displaced by one equivalent of the polarisable bromide or chloride ion to regenerate the non-ionic aurous complex (I; X = Br or Cl respectively). Whilst therefore Smith's conductivity experiments referred to above did not establish beyond doubt the non-existence of salts of type (V), his observation that the dichloride itself was non-conducting in chloroform solution showed a salt-like structure to be unlikely. This is supported by a similar finding by Ray and Sen (*loc. cit.*) that the acetone solution of the same compound is non-conducting when first prepared although it slowly acquires an increasing conductivity, presumably owing to decomposition.

In the present work, incidental to which a further compound of the same type—benzyl sulphide–bromoiodogold, $(C_7H_7)_2S,AuBrI$—has been isolated, the dibromide has been re-investigated both in the solid state and in solution, and the dichloride and the dibromide have been subjected to *X*-ray examination. The evidence described below indicates that these substances neither contain bivalent gold nor are true compounds of types (I) and (II) but that they are lattice compounds in the solid state in which, as also in solution, (I) and (II) exist as separate discrete entities. Since the compounds all melt at about 130° with gross decomposition a thermal investigation was not possible.

Molecular Weight.—The molecular weights of the dihalides, determined cryoscopically in bromoform (method of Roberts and Bury, *J.*, 1923, **123**, 2037), or in benzene, are the same as the formula weights. This does not distinguish between true dihalides and substances composed of equimolecular proportions of types (I) and (II), but does show the observations by Hermann and by Ray and Sen to be in error and provides further evidence that the compounds under consideration cannot be (III or IV; X = Br, Cl).

Electrical Conductivity.—Solutions of the same compounds in nitrobenzene have been found to be non-conducting, which confirms the observations by Hermann and by Ray and Sen and their conclusions that the dihalides are not ionic compounds.

Magnetic Susceptibility.—In consequence of the odd atomic number of gold, compounds containing one atom of this element in which it exerts a valency of two must of necessity contain an odd number of electrons and hence be paramagnetic. Elliott (*J. Chem. Phys.*, 1934, **2**, 419) has made use of this to show that the black crystalline compound of empirical formula $CsAuCl_3$ cannot contain bivalent gold since it is diamagnetic ($\chi = -0{\cdot}25 \times 10^{-6}$ e.m.u.), concluding that it must be a lattice compound of $CsAuCl_2$ and $CsAuCl_4$, as was later confirmed by Elliott and Pauling (*J. Amer. Chem. Soc.*, 1938, **60**, 1848). An examination of benzyl sulphide–mono-, di-, and tri-bromogold by the Gouy method has revealed that these are all diamagnetic in the solid state with $\chi = -0{\cdot}48$, $-0{\cdot}33$, and $-0{\cdot}36 \times 10^{-6}$ e.m.u. respectively, but little greater than the value quoted above and that of $-0{\cdot}23 \times 10^{-6}$ e.m.u. reported by Burawoy and Gibson (*J.*, 1935, 218) for Au_2Br_6, showing conclusively the absence of bivalent gold from the solid dibromide.

Rate of Reduction in Solution.—Benzyl sulphide–di- and tri-bromogold are reduced by acetone or styrene with or without chloroform as solvent, and this reaction has been investigated kinetically in an attempt to show some difference in behaviour of the two compounds. For this purpose acetone was unsatisfactory (*a*) because the reaction came to equilibrium (colourless acetone solutions of benzyl sulphide–monobromogold containing hydrogen bromide and monobromoacetone slowly developed the colour characteristic of the di- or tri-bromide) and (*b*) because of the production of free acid, the catalytic effect of which on the halogenation of acetone is well known, and of bromide ion which is known to influence the rate of somewhat similar reactions, *e.g.*, the disproportionation of benzyl sulphide–monobromogold :

$$3(C_7H_7)_2S,AuBr \longrightarrow (C_7H_7)_2S,AuBr_3 + 2Au + (C_7H_7)_2S$$

Styrene was therefore selected as reducing agent. In chloroform solution containing a large molecular excess of styrene, benzyl sulphide–tribromogold was reduced smoothly and completely according to the first-order law, the rate being proportional to the styrene concentration over the range investigated.

Parallel experiments were performed under identical conditions at two temperatures with solutions containing twice the molecular concentration of benzyl sulphide–dibromogold [taken as $(C_7H_7)_2S,AuBr_2$] as of benzyl sulphide–monobromogold, *i.e.*, containing the *same* initial concentration of tribromo-compound in each case on the assumption that the dibromide existed as mono- and tri-bromide in solution. The concentrations of styrene were adjusted according to the conditions to give reasonable rates of reduction, and the progress of the reaction was followed by titrating aliquot portions with sodium thiosulphate solution as described in the Experimental section. At each temperature, in the plot of log titre against time the points for both compounds lie about the same straight line, the results of typical experiments being illustrated in Fig. 1. Thus the solution of the dibromide behaved exactly as would be expected of a solution containing equivalent amounts of mono- and tri-bromide, the activation energy of the reduction hence being the same in each case. Before accepting this evidence of the non-existence of benzyl sulphide–dibromogold in solution it must not be overlooked that the same results would have been obtained if, in the presence of so large an excess of styrene, the benzyl sulphide had been displaced from each compound to give, as common intermediate, a styrene complex of which the rate of further reaction was that measured in each case, *e.g.* :

$$(C_7H_7)_2S,AuBr_3 + C_8H_8 \longrightarrow C_8H_8,AuBr_3 + (C_7H_7)_2S$$
$$2(C_7H_7)_2S,AuBr_2 + C_8H_8 \longrightarrow C_8H_8,AuBr_3 + (C_7H_7)_2S + (C_7H_7)_2S,AuBr$$
$$C_8H_8,AuBr_3 \longrightarrow \text{Products}$$

This possibility, however, was rejected since the addition of a few drops of styrene to a chloroform suspension of tribromogold, which would be expected to cause reduction at a rate roughly comparable with, and in any case, in view of the insolubility of tribromogold, not greater than, that for benzyl sulphide–tribromogold, resulted in the *immediate* reduction of the compound to metallic gold. If such a styrene complex were formed as an unstable intermediate, as further evidence suggested was indeed the case, it would therefore not be

expected that its further decomposition would be the rate-determining stage of the reaction. That such an intermediate is formed is supported by the further observation that the addition of small amounts of benzyl sulphide to the reaction mixture caused the rate of reduction of benzyl sulphide–tribromogold to fall, clearly indicating that in one stage of the reaction benzyl sulphide is disengaged reversibly. The effect was quantitatively the same on the rate of reduction of the dibromide (Fig. 2). The stages of the reactions are therefore considered to be :

$$(C_7H_7)_2S,AuBr_3 + C_8H_8 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C_8H_8,AuBr_3 + (C_7H_7)_2S$$

$$C_8H_8,AuBr_3 \xrightarrow[k_3\ (fast)]{} \text{Products}$$

in which the overall rate of reduction would be determined by the rate of formation of the styrene complex; that being so, it is difficult to escape the conclusion that the reactions

FIG. 1. *Reduction by styrene at 25° (I) and at 35° (II) of equivalent amounts of benzyl sulphide–tribromogold ◐ and ◑, and benzyl sulphide–dibromogold ○ and △.*

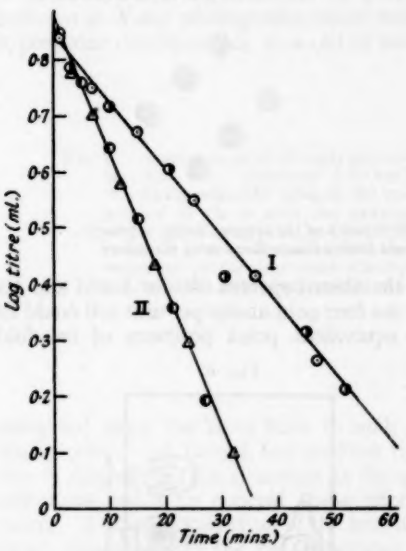
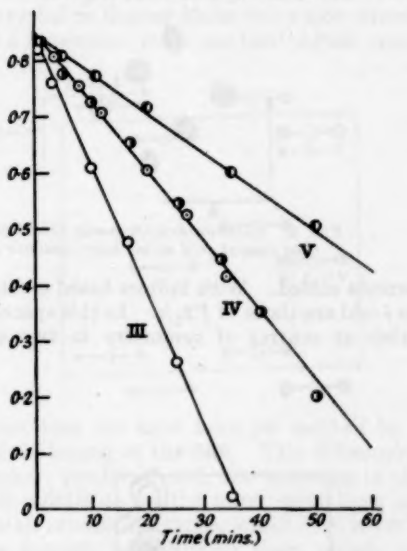


FIG. 2. *Effect on reaction rate of added benzyl sulphide : III, nil ; IV, 0·1 g. ; V, 0·5 g. Benzyl sulphide–tribromogold : ○, ○. Benzyl sulphide–dibromogold : ◐, ◑.*



are identical with the two compounds and that therefore solutions of the " dibromide " contain equimolecular amounts of benzyl sulphide–mono- and tri-bromogold. The above mechanism leads to the expression :

$$v = (k_1k_3[C_8H_8][(C_7H_7)_2S,AuBr_3])/(k_2[(C_7H_7)_2S] + k_3)$$

for the overall rate of reaction, which, for constant concentrations of styrene and benzyl sulphide, reduces to a first-order relation. It is clear therefore that benzyl sulphide cannot accumulate in the reaction mixture but must rapidly reach a steady value, as would be accounted for by its recombination with aurous bromide, resulting from the reduction, to give benzyl sulphide–monobromogold which is not susceptible to further attack by styrene.

Hitherto, no evidence has been provided for the existence even momentarily of compounds of gold with unsaturated hydrocarbons, but such compounds of ethylene with platinous halides are well known and it is interesting that the electronic configuration of platinum in these and of gold in the styrene complex, the existence of which is postulated above, would be identical, on the assumption that the method of linkage of the unsaturated hydrocarbon is the same in each case.

Magnetic Susceptibility.—In consequence of the odd atomic number of gold, compounds containing one atom of this element in which it exerts a valency of two must of necessity contain an odd number of electrons and hence be paramagnetic. Elliott (*J. Chem. Phys.*, 1934, **2**, 419) has made use of this to show that the black crystalline compound of empirical formula $CsAuCl_3$ cannot contain bivalent gold since it is diamagnetic ($\chi = -0{\cdot}25 \times 10^{-6}$ e.m.u.), concluding that it must be a lattice compound of $CsAuCl_2$ and $CsAuCl_4$, as was later confirmed by Elliott and Pauling (*J. Amer. Chem. Soc.*, 1938, **60**, 1848). An examination of benzyl sulphide–mono-, di-, and tri-bromogold by the Gouy method has revealed that these are all diamagnetic in the solid state with $\chi = -0{\cdot}48$, $-0{\cdot}33$, and $-0{\cdot}36 \times 10^{-6}$ e.m.u. respectively, but little greater than the value quoted above and that of $-0{\cdot}23 \times 10^{-6}$ e.m.u. reported by Burawoy and Gibson (*J.*, 1935, 218) for Au_2Br_6, showing conclusively the absence of bivalent gold from the solid dibromide.

Rate of Reduction in Solution.—Benzyl sulphide–di- and tri-bromogold are reduced by acetone or styrene with or without chloroform as solvent, and this reaction has been investigated kinetically in an attempt to show some difference in behaviour of the two compounds. For this purpose acetone was unsatisfactory (*a*) because the reaction came to equilibrium (colourless acetone solutions of benzyl sulphide–monobromogold containing hydrogen bromide and monobromoacetone slowly developed the colour characteristic of the di- or tri-bromide) and (*b*) because of the production of free acid, the catalytic effect of which on the halogenation of acetone is well known, and of bromide ion which is known to influence the rate of somewhat similar reactions, *e.g.*, the disproportionation of benzyl sulphide–monobromogold :

$$3(C_7H_7)_2S,AuBr \longrightarrow (C_7H_7)_2S,AuBr_3 + 2Au + (C_7H_7)_2S$$

Styrene was therefore selected as reducing agent. In chloroform solution containing a large molecular excess of styrene, benzyl sulphide–tribromogold was reduced smoothly and completely according to the first-order law, the rate being proportional to the styrene concentration over the range investigated.

Parallel experiments were performed under identical conditions at two temperatures with solutions containing twice the molecular concentration of benzyl sulphide–dibromogold [taken as $(C_7H_7)_2S,AuBr_2$] as of benzyl sulphide–monobromogold, *i.e.*, containing the *same* initial concentration of tribromo-compound in each case on the assumption that the dibromide existed as mono- and tri-bromide in solution. The concentrations of styrene were adjusted according to the conditions to give reasonable rates of reduction, and the progress of the reaction was followed by titrating aliquot portions with sodium thiosulphate solution as described in the Experimental section. At each temperature, in the plot of log titre against time the points for both compounds lie about the same straight line, the results of typical experiments being illustrated in Fig. 1. Thus the solution of the dibromide behaved exactly as would be expected of a solution containing equivalent amounts of mono- and tri-bromide, the activation energy of the reduction hence being the same in each case. Before accepting this evidence of the non-existence of benzyl sulphide–dibromogold in solution it must not be overlooked that the same results would have been obtained if, in the presence of so large an excess of styrene, the benzyl sulphide had been displaced from each compound to give, as common intermediate, a styrene complex of which the rate of further reaction was that measured in each case, *e.g.* :

$$(C_7H_7)_2S,AuBr_3 + C_8H_8 \longrightarrow C_8H_8,AuBr_3 + (C_7H_7)_2S$$
$$2(C_7H_7)_2S,AuBr_2 + C_8H_8 \longrightarrow C_8H_8,AuBr_3 + (C_7H_7)_2S + (C_7H_7)_2S,AuBr$$
$$C_8H_8,AuBr_3 \longrightarrow \text{Products}$$

This possibility, however, was rejected since the addition of a few drops of styrene to a chloroform suspension of tribromogold, which would be expected to cause reduction at a rate roughly comparable with, and in any case, in view of the insolubility of tribromogold, not greater than, that for benzyl sulphide–tribromogold, resulted in the *immediate* reduction of the compound to metallic gold. If such a styrene complex were formed as an unstable intermediate, as further evidence suggested was indeed the case, it would therefore not be

expected that its further decomposition would be the rate-determining stage of the reaction. That such an intermediate is formed is supported by the further observation that the addition of small amounts of benzyl sulphide to the reaction mixture caused the rate of reduction of benzyl sulphide–tribromogold to fall, clearly indicating that in one stage of the reaction benzyl sulphide is disengaged reversibly. The effect was quantitatively the same on the rate of reduction of the dibromide (Fig. 2). The stages of the reactions are therefore considered to be :

$$(C_7H_7)_2S,AuBr_3 + C_8H_8 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C_8H_8,AuBr_3 + (C_7H_7)_2S$$

$$C_8H_8,AuBr_3 \xrightarrow[k_3\ (fast)]{} \text{Products}$$

in which the overall rate of reduction would be determined by the rate of formation of the styrene complex; that being so, it is difficult to escape the conclusion that the reactions

FIG. 1. *Reduction by styrene at 25° (I) and at 35° (II) of equivalent amounts of benzyl sulphide–tribromogold ◐ and ◑, and benzyl sulphide–dibromogold ○ and △.*

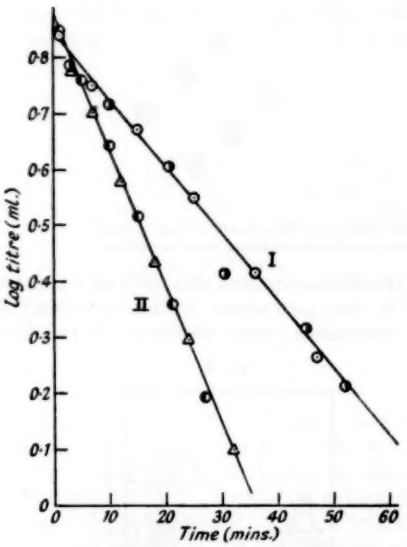
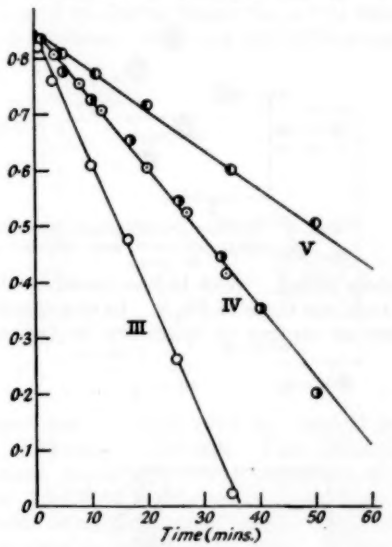


FIG. 2. *Effect on reaction rate of added benzyl sulphide : III, nil ; IV, 0·1 g. ; V, 0·5 g. Benzyl sulphide–tribromogold : ⊙, ○. Benzyl sulphide–dibromogold : ◐, ◑.*



are identical with the two compounds and that therefore solutions of the " dibromide " contain equimolecular amounts of benzyl sulphide–mono- and tri-bromogold. The above mechanism leads to the expression :

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X-*Ray Investigation.*—The constitutions of the compounds $(C_7H_7)_2SAuCl_2$ and $(C_7H_7)_2SAuBr_2$ have been found from the examination of their crystal structures. The two compounds form related structures but are not isomorphous. For the chloride the apparent monoclinic unit cell dimensions are $a = 5{\cdot}66$, $b = 19{\cdot}79$, $c = 13{\cdot}39$ Å, $\beta = 92°$. The density is 2·1 g./c.c. and the unit cell contains atoms corresponding to four times the

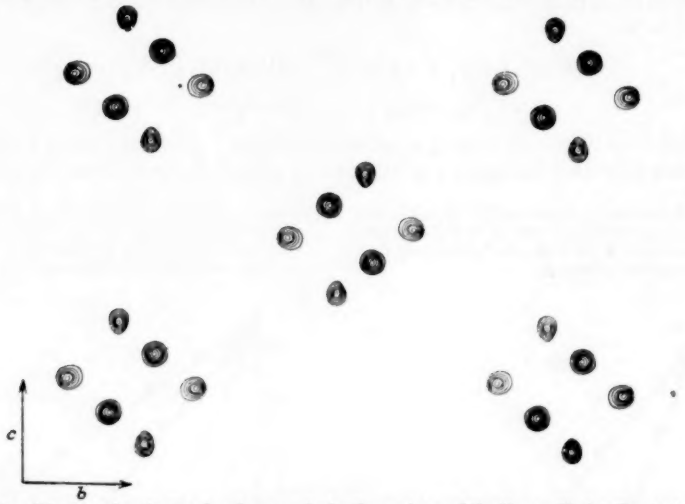


FIG. 3. *Electron-density peaks shown only in the regions of the linear* Cl–Au–S *groups. The central gold atoms have contours at intervals twelve times those used elsewhere.*

formula stated. With indices based on this cell the absent spectra $0k0$ for k odd and $h0l$ for l odd are those of $P2_1/c$. In this space-group the four gold atoms per unit cell could lie either at centres of symmetry in two sets of equivalent point positions of two-fold

FIG. 4.

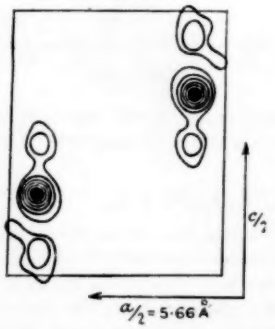
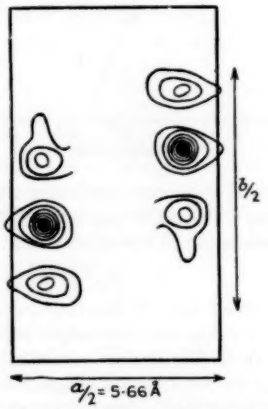


FIG. 5.



FIGS. 4. and 5. *Electron-density peaks shown only in the region of the linear* Cl–Au–S *groups.*

multiplicity or in the general point positions of four-fold multiplicity with co-ordinates : $x\,y\,z$; $\bar{x}\,\bar{y}\,\bar{z}$; $\bar{x}$, $\frac{1}{2}+y$, $\frac{1}{2}-z$; x, $\frac{1}{2}-y$, $\frac{1}{2}+z$. The first of these possibilities, which need not be rejected on any uncertain chemical grounds, requires a set of structure factors entirely at variance with the observed F_{hk0}, F_{h0l}, and F_{0kl} values, but consistent values of xyz for gold atoms in the general positions may be readily obtained by F^2 and F Fourier

synthesis in three independent projections. With the co-ordinates then found the main characteristics of the observed F values are reproduced in approximate calculated values which take into account only the gold contributions.

In accordance with the space-group symmetry the four gold atoms would be in every way equivalent and each could therefore be the central atom of a molecule $(C_7H_7)_2SAuCl_2$, but any formula such as $[\{(C_7H_7)_2S\}_2Au]^+AuCl_4^-$ designed to avoid bivalent gold by the introduction of two dissimilar gold atoms would be impossible. Thus not merely the conclusions drawn from unit cell and space-group symmetry, but also a determination of the co-ordinates for the gold atoms, seem to indicate that the compound contains bivalent gold. This conclusion, however, is false and it arises from a combination of accidental circumstances which are revealed when attempts are made to determine the structure in greater detail. In order to establish the existence of bivalent gold it is necessary to determine the positions of the sulphur and the two chlorine atoms supposedly attached to the gold. Failure of the subsequent stages of the Fourier analysis to reveal more than two of the required atoms led to a re-examination of all the assumptions made and to further *X*-ray examination with prolonged exposures. It was thus found that the structure must be based on a unit cell of double the *a* dimension with eight molecules per unit cell. This is shown in *X*-ray photographs taken with the crystal oscillating about the *a* axis where, in positions corresponding to a cell of twice the *a* dimension, there are faint diffuse spots

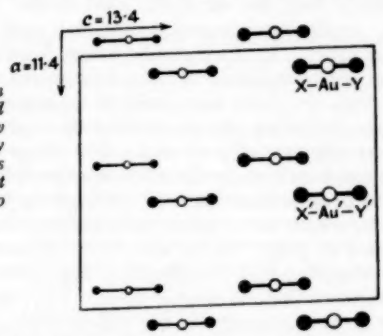


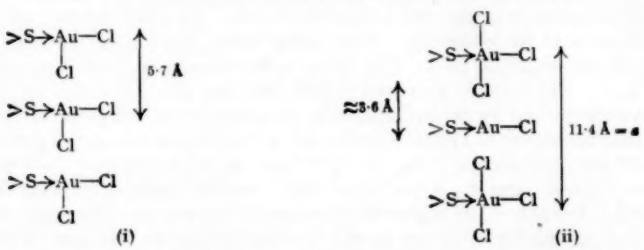
FIG. 6. *Arrangement of the eight gold atoms in the unit cell. Alternate* >S·AuCl *and* >S·AuCl$_2$ *molecules lying in the same row parallel to the* a *axis are indicated by circles of the same size, and the differences in circle size are intended to convey that molecules in the four rows illustrated do not lie at the same depth within the cell.*

elongated along the layer lines to such an extent that the layer lines are marked by a nearly continuous though not uniform region of darkening of the film. This diffuseness, due to disorder in the structure as discussed below, combined with the weakness of the reflections tends to conceal these effects. All reflections on the other layer lines are sharp. *X*-Ray examination of the bromide crystals reveals differences which complicate a direct comparison of the two structures but the bromide has a similar short pseudo-cell spacing of 5·7 Å. Intermediate diffuse layer lines, stronger than those of the chloride, indicate a similar doubling of the cell in this direction. In what follows all indices refer to the cell with $a = 11{\cdot}32$ (chloride). They differ from those relating to the pseudo-cell $a = 5{\cdot}66$ only in the doubling of h. The sharp reflections have, as before, the systematic absences of $P2_1/c$. The further absences of $h00$, $h0l$, and $hk0$ for h odd do not arise from space-group symmetry but from similarities in co-ordinates of different atoms.

The eight gold atoms of the cell consist of two sets of four atoms in the general positions, 4Au in xyz and its equivalents, 4Au′ in $x'y'z'$ and its equivalents. To account for the pseudo-cell $y = y'$, $z = z'$, and $x = \frac{1}{2} + x'$ must hold. Similar relations hold for the two atoms attached to gold. In each of the three electron-density projections the peaks corresponding to these atoms, *e.g.*, sulphur and one of the chlorine atoms in the case of the dichloride (Figs. 3, 4, and 5), are seen to be in a straight line and these three atoms must therefore form a *linear* group. The absence of peaks high enough to represent the other chlorine atoms is discussed below. Satisfactory positions for the benzyl groups may be inferred from space considerations but since they do not affect the present argument they are not considered here. The arrangement of the eight X–Au–Y groups in the cell is shown in Fig. 6.

The projections derived from observed F_{h0l} and F_{hk0} necessarily have the pattern repeating by translation at $a/2$ (5·7 Å) and cannot distinguish atoms of types Au and Au′. This is because the terms with h odd cannot be included, there being no sharp reflections to correspond, and no further progress is possible with these projections. In the third projection F_{0kl} values alone are used; there is no such omission of terms and, in principle, all atoms could show up separately; but in this projection there is a complete atom-for-atom overlap of X–Au–Y and X′–Au′–Y′. Here also, but for a different reason, the presence of the two groups of atoms cannot be demonstrated. Three-dimensional Fourier analysis which could resolve the difficulty cannot be made owing to the impossibility of observing F_{hkl} with h odd, the corresponding spots being diffuse; it is precisely these values of F that would introduce any distinctions between the two groups. In these difficult circumstances it is still possible to determine enough of the structure for the present purpose. This may be done by use of the information of both positive and negative kinds in the projections, and by a comparison of the chloride and bromide.

Although the bromide structure as a whole is somewhat different, the zero layer line Weissenberg photographs for rotation about the 5·7 (pseudo-cell) axis show a marked resemblance, and the corresponding patterns seen in projection have the overlapping X and X′ peak about twice as high as that for the overlapping Y and Y′. This can only be so if X and X′ are both bromine and Y and Y′ are both sulphur atoms. This excludes the possibility that the alternate gold atoms are those of $[(C_7H_7)_2S\rightarrow Au\leftarrow S(C_7H_7)_2]^+$ and $AuBr_4^-$ groups since in such a case each peak would be due to a bromine and an overlapping sulphur atom. In the chloride, where X and Y have approximately the same peak height, there is good resolution of these two atoms attached to each gold but in none of the three projections are there any peaks to represent the second chlorine although there is ample evidence, including the projections themselves, that the observed F's and their calculated signs are substantially correct. The 0kl projection is not influenced by the disorder that affects the h indices, and in this case the only possible explanation for the lack of the other chlorine peak is that there is overlapping with the gold atom. This is confirmed in the bromide, where the relative peak heights show that the second bromine atom is similarly concealed by gold. In the other two chloride projections, where the second chlorine does not overlap, the lack of sufficiently high peaks is due to the disorder effect indicated by the diffuseness of the odd h layer lines. That the halogen is involved in the disorder is shown by the greater intensity of the diffuse spots in the bromide. Chlorine atoms are therefore fixed on lines joining Au . . . Au . . . Au and occupy alternative positions in such a way that no position holds statistically more than about $\frac{1}{2}$Cl and consequently there is no peak comparable with those of sulphur and chlorine. One chlorine atom must be inserted somewhere between each pair of gold atoms, and since even the mid-point is only 2·83 Å from the gold atom this chlorine atom is considerably closer than the separations to be expected for ions or unlinked atoms. It must therefore be linked by a covalency to one atom, at about 2·1 Å. This leaves a satisfactory space of 3·56 Å between it and the other



gold neighbour to which it is not linked. If the structure were represented by the atomic arrangement (i), a disorder effect could be obtained by placing chlorine atoms above instead of below gold atoms in some rows, but the repeat distance along a would be 5·7 Å. Neither the sharp reflections nor the diffuse layer lines corresponding to $a = 11{\cdot}4$ are explained by this arrangement. They are, however, explained by the structure (ii), in which alternate

gold atoms have valencies 1 and 3. The unit repeat distance is clearly 11·4 Å and the disorder arises through . . Au . . . Au′ . . . Au . . rows' being displaced by 5·7 Å along *a* so that in different unit cells a given point position may be occupied equally well by Au or Au′. In projections which contain the Au . . . Au′ . . line every gold atom will therefore have adjacent to it two positions each occupied statistically by $\frac{1}{2}$Cl. This corresponds in electron density to little more than a CH group and therefore in the presence of benzyl groups does not show up in the same clear manner as the single chlorine atom.

The structure consists of $(C_7H_7)_2SAuCl$ and $(C_7H_7)_2SAuCl_3$ molecules, both of which can be readily formulated in accordance with the common valency behaviour of gold and are known to exist separately. The compound does not contain bivalent gold but is a crystalline molecular compound of these two substances.

Experimental

Unless otherwise stated all the compounds described below melted with decomposition at or about 130°. Analyses were carried out by Drs. Weiler and Strauss, Oxford.

Benzyl Sulphide–Dichlorogold.—This was prepared as described by Hermann (*Ber.*, 1905, **38**, 2813) and recrystallised from chloroform containing a little benzyl sulphide. The compound was obtained in the fiery orange needles he describes [Found: Au, 40·8%; *M* (cryoscopic) in benzene, 500; in bromoform, 473. Calc. for $C_{14}H_{14}Cl_2SAu$: Au, 40·9%; *M*, 482]. A solution of the compound in nitrobenzene, examined in a Mullard conductivity apparatus, type E7566, was non-conducting.

Benzyl Sulphide–Monobromogold.—This was prepared from the hydrobromoaurous acid reagent described by Brain, Gibson, and Imperial Chemical Industries Limited (B.P. 497,746). A warm solution of potassium bromoaurate (5 g.) in ethanol (25 ml.) containing a little water was reduced by addition of an ethanolic solution of sulphur dioxide until colourless, and benzyl sulphide (2 g.) in warm ethanol (15 ml.) added at once. A colourless oil separated which rapidly solidified on being stirred. After being cooled thoroughly, the solid was collected, washed with water, dried over concentrated sulphuric acid, and recrystallised by dissolution in chloroform, containing a little benzyl sulphide, on the water-bath, filtration, and addition of ligroin (b. p. 60—80°) until crystallisation set in. Long colourless needles of benzyl sulphide–monobromogold (3·78 g., 91%) slowly separated. These were collected, washed with a 1 : 1 mixture of chloroform–ligroin (b. p. 60—80°), and dried in air [Found: Au, 40·1%; *M* (cryoscopic) in bromoform, 492. Calc. for $C_{14}H_{14}BrSAu$: Au, 40·1%; *M*, 491]. A solution of the compound in nitrobenzene examined as above was non-conducting.

Benzyl Sulphide–Tribromogold.—Benzyl sulphide–monobromogold (1 g.) in warm chloroform (5 ml.) was treated with bromine in carbon tetrachloride (9·4 ml. of 0·435N-solution = 2 equiv.). The resulting deep red solution gradually deposited dark ruby-red crystals (0·9 g., 81%) of *benzyl sulphide–tribromogold*, which were collected, washed with carbon tetrachloride, and dried in air [Found: Au, 30·0; Br, 36·7%; *M* (cryoscopic) in benzene, 654. $C_{14}H_{14}Br_2SAu$ requires Au, 30·3; Br, 36·8%; *M*, 651]. A solution of the compound in nitrobenzene examined as above was non-conducting.

Benzyl sulphide–dibromogold was prepared somewhat unsatisfactorily by Smith (*loc. cit.*) by the action of benzyl sulphide on an ethereal solution of hydrobromoauric acid. We obtained it very simply by the method employed above for the tribromo-compound, using one half the proportion of bromine.

Benzyl sulphide–monobromogold (1·36 g.) was dissolved in warm chloroform (10 ml.) and treated with bromine in carbon tetrachloride (3·4 ml. of 0·82N-solution = 1 equiv.). The deep red solution rapidly deposited brown needles (1·48 g., 93%) of benzyl sulphide–dibromogold, which were collected, washed with carbon tetrachloride, and dried in air. The compound recrystallised from warm chloroform containing benzyl sulphide, but as prepared was pure [Found: Au, 34·5; Br, 27·6%; *M* (cryoscopic) in bromoform, 584. Calc. for $C_{14}H_{14}Br_2SAu$: Au, 34·5; Br, 28·0%; *M*, 571]. A solution of the compound in nitrobenzene examined as above was non-conducting.

This substance was also obtained by the interaction of benzyl sulphide–mono- and –tribromide in solution in the same way as for the dichloride (Ray and Sen, *loc. cit.*). Benzyl sulphide–monobromogold (0·47 g.) was dissolved in warm chloroform (3 ml.) containing a little benzyl sulphide and mixed with a solution of benzyl sulphide–tribromogold (0·63 g., 1 mol.) in warm chloroform (12 ml.) also containing a little benzyl sulphide. Pure benzyl sulphide–dibromogold (0·75 g.) gradually crystallised, identical in appearance with that obtained as above (Found: Au, 34·5%).

Benzyl Sulphide–Bromoiodogold.—A solution of iodine (0·8 g., one equiv.) in chloroform was added to benzyl sulphide–monobromogold (3·8 g.) in chloroform (30 ml.), and the mixture set aside. The almost black crystals (3·9 g.) which separated were collected, washed with a little chloroform, and dried in air. Recrystallisation from chloroform gave pure *benzyl sulphide–bromoiodogold* (Found: Au, 32·0; Br + I, 33·6; S, 5·4. $C_{14}H_{14}BrISAu$ requires Au, 31·9; Br + I, 33·5; S, 5·2%).

Di(benzyl sulphide)–Aurous Nitrate.—Benzyl sulphide–monobromogold (2·15 g.) and benzyl sulphide (1·2 g.) were dissolved in warm chloroform (20 ml.) and vigorously shaken in a stoppered bottle with finely powdered silver nitrate (0·75 g.) for 15 minutes. The solution was filtered, the residue washed with a little warm chloroform, and the combined filtrate allowed to evaporate slowly in a dry atmosphere. Colourless transparent prisms (2·12 g.), m. p. 104—107° (decomp.), of *di(benzyl sulphide)–aurous nitrate* separated, which were collected, washed with chloroform, and dried. In the air the crystals became opaque owing to loss of chloroform of crystallisation and when kept they slowly darkened (Found, on freshly prepared material: Au, 24·3; on material dried to constant wt.: C, 48·2; H, 4·2; Au, 28·3. $C_{28}H_{28}O_3NS_2Au,CHCl_3$ requires Au, 24·4. $C_{28}H_{28}O_3NS_2Au$ requires C, 48·9; H, 4·1; Au, 28·7%). This substance was insoluble in water, acetone, and ligroin but dissolved in methanol, ethanol, chloroform, and acetic acid, such solutions depositing gold when heated. Pyridine displaced benzyl sulphide from it in the cold, as did aqueous solutions of potassium bromide and sodium chloride.

The compound (0·5 g.) was shaken with chloroform (5 ml.) and a solution of potassium bromide (0·075 g.) in water (1 ml.) until all had dissolved. The chloroform layer was separated and after being dried (Na_2SO_4) was treated with ligroin (b. p. 60—80°) until crystallisation set in. The crystalline product proved to be benzyl sulphide–monobromogold (0·28 g., theor., 0·30 g.) (Found: Au, 40·0. Calc. for $C_{14}H_{14}BrSAu$: Au, 40·1%).

Repetition of this experiment with an equivalent (0·04 g.) of sodium chloride in place of potassium bromide gave benzyl sulphide–monochlorogold (0·24 g.; theor., 0·28 g.) (Found: Au, 44·1. Calc. for $C_{14}H_{14}ClSAu$: Au, 44·1%).

Di(benzyl sulphide)–Aurous Perchlorate.—This was obtained as described, by the action of solid silver perchlorate (0·4 g.) on benzyl sulphide–monobromogold (0·87 g.) and benzyl sulphide (0·42 g.) in warm chloroform (15 ml.). The perchlorate was somewhat less soluble than the nitrate and it was necessary to extract the insoluble silver salts several times with warm chloroform to remove that part which crystallised out during the reaction. The filtered chloroform solution gave colourless prisms of *di(benzyl sulphide)–aurous perchlorate* (0·57 g.), m. p. 140° (decomp.), on slow evaporation. These, like the nitrate, became opaque owing to loss of chloroform of crystallisation (Found, on freshly prepared material: Au, 23·2; on material dried to constant wt.: Au, 27·2; C, 46·9; H, 4·2. $C_{28}H_{28}O_4ClS_2Au,CHCl_3$ requires Au, 23·3. $C_{28}H_{28}O_4ClS_2Au$ requires Au, 27·2; C, 46·4; H, 3·9%).

Reaction Rate Experiments.—Approx. 10^{-3} mole of benzyl sulphide–tribromogold and exactly twice this amount of the dibromo-compound [*i.e.*, *ca.* 2×10^{-3} mole taken as $(C_7H_7)_2S,AuBr_3$] were used for each pair of experiments. The gold compound was dissolved in, and made up to 100 ml. with, chloroform which had been dried over potassium carbonate and redistilled. Commerical styrene was redistilled under reduced pressure and kept in the dark at −5°. The chosen volume of styrene was diluted with the same chloroform to 100 ml. and the two solutions were left in the thermostat for 30 minutes before being mixed. At intervals, 20 ml. of the mixture were withdrawn by pipette and run into 10 ml. of 40% (w/v) aqueous potassium thiocyanate in a stoppered bottle, which was then shaken vigorously for 20 seconds. This stopped the reaction by precipitating the remaining auric gold in the form of a salmon-coloured compound, the nature of which was not investigated. The compound was somewhat soluble in the aqueous phase but sparingly so in the chloroform and the amount of unreduced gold was determined by titration with approx. N/40-sodium thiosulphate, with vigorous shaking after each addition, until all the precipitate had redissolved and the last trace of salmon colour had disappeared from the aqueous layer. Experiment showed that in this titration one molecule of benzyl sulphide–tribromogold required exactly two molecules of thiosulphate.

The authors thank Dr. R. S. Nyholm for making the measurements of the magnetic susceptibilities, and one of them (A. T.) gratefully acknowledges a grant from Imperial Chemical Industries Limited.

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708. *Studies on Unimolecular Chlorohydrocarbon Decompositions. Part II.**

By K. E. Howlett.

The homogeneous thermal decompositions of ethyl chloride, ethylidene dichloride, and *iso*propyl chloride have been studied at low pressures. All three reactions are unimolecular, their rate constants being pressure-dependent below a certain critical pressure in each case. The order of reaction with ethylidene dichloride was perceptibly above 1 at the lowest pressures studied. The results have been examined from the point of view of the theories of Rice and Ramsperger, and are in accord with the idea that the transformation probability of an activated molecule is a function of the energy in excess of the minimum required for reaction.

The marked differences between the homogeneous first-order decompositions of 1 : 2-dichloroethane (Barton and Howlett, *J.*, 1949, 155; Howlett, *Nature*, 1950, **165**, 860; *Trans. Faraday Soc.*, 1952, **48**, 25), the tetrachloroethanes (Barton and Howlett, *J.*, 1951, 2033), and 2 : 2′-dichlorodiethyl ether (Barton, Head, and Williams, *J.*, 1951, 2039) on the one hand, and those of ethyl chloride, 1 : 1-dichloroethane (Barton and Howlett, *J.*, 1949, 165), and the monochloro-propanes and -butanes (Barton and Head, *Trans. Faraday Soc.*, 1950, **46**, 114; Barton, Head, and Williams, *loc. cit.*; Barton and Onyon, *Trans. Faraday Soc.*, 1949, **45**, 725; Howlett, to be published) on the other, leaves little alternative explanation for the mechanism of the latter reactions but that they are unimolecular processes. The evidence already presented in support of this contention includes lack of sensitivity towards small additions of oxygen and chlorine, and complete insensitivity to chain-inhibiting substances such as propylene. Furthermore, good first-order velocity constants are obtained right from zero time (showing absence of induction periods) and for large percentages of conversion, over considerable pressure ranges. It is well known, however, that any theory of unimolecular reactions, such as Lindemann and Hinshelwood's mechanism (*Trans. Faraday Soc.*, 1922, **17**, 598), demands the existence of a critical pressure region, below which the Maxwell–Boltzmann distribution of energies is not maintained. This should be manifest in a lowering of the rate constant and a change over towards second-order kinetics, and these two effects have been considered the most important qualitative characteristics of unimolecular reactions (cf. Ramsperger, *Chem. Reviews*, 1932, **10**, 27).

In the present investigation, therefore, three representatives of the apparently 100% unimolecular decompositions have been studied at low pressures, both to confirm our ideas on their mode of reaction and then, with their aid, to examine theories of unimolecular reactions. These theories, although well advanced, have mainly been applied to reactions such as the decompositions of nitrous oxide, dinitrogen pentoxide, and azomethane, which, as emphasised in a preliminary note (*Nature*, in the press; cf. Pease, *J. Chem. Physics*, 1939, **7**, 749), are not now considered to be simple unimolecular reactions.

Experimental

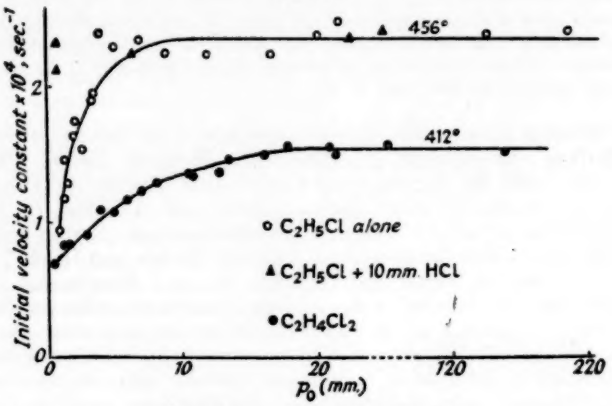
Materials and Apparatus.—Ethyl chloride, 1 : 1-dichloroethane, and *iso*propy lchloride were purified as described in previous publications. The following physical constants were measured : ethyl chloride, b. p. 12·4$_5$°; 1 : 1-dichloroethane, b. p. 57·3° (corr.), n_D^{20} 1·4170; *iso*propyl chloride, b. p. 34·8° (corr.), n_D^{20} 1·3782. Critical compilations of these constants are available in the relevant previous publication and in Timmermans, " Physico-Chemical Constants of Pure Organic Compounds," Elsevier, 1950.

In essentials, the apparatus employed was similar to that described by Barton and Howlett (*J.*, 1949, 155). The Pyrex-glass spoon gauges used have permitted readings to be taken to 0·01 mm. of mercury. All results reported refer to decompositions in a reactor of surface/volume ratio 2 cm.$^{-1}$, and whose surface has been aged by covering it with a carbonaceous film through storage in prolonged contact with the reaction products at 450—500°.

* Barton and Howlett, *J.*, 1949, 165, is considered to be Part I of this series.

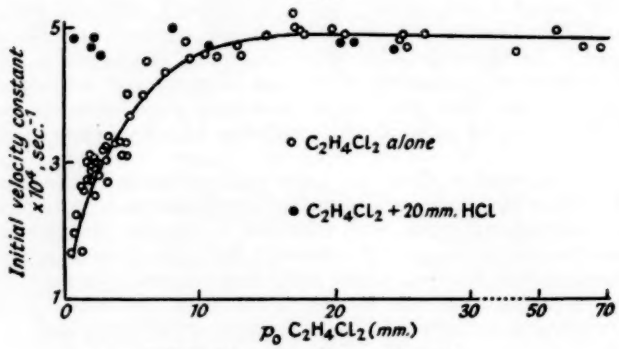
Results.—Ethyl chloride. Barton and Head (*loc. cit.*) reported a recalculated velocity constant for this decomposition of $k = 10^{14\cdot6}\,e^{-60,800/RT}$ sec.$^{-1}$, and this is unvarying (Barton and Howlett, *J.*, 1949, 165) over the pressure range 20—200 mm. In the present study, the pyrolysis of ethyl chloride has been examined at 456°. Fig. 1 shows the decomposition rate constant as a function of the initial pressure (p_0). At higher pressures (>8 mm.) the mean velocity constant (236 × 10^{-6} sec.$^{-1}$) agrees well with that found previously (235 × 10^{-6} sec.$^{-1}$). Below 8 mm. the rate constant falls below its high-pressure value. (In Figs. 1—4, the low-pressure velocity constants plotted, are the initial velocity constants calculated as first order.)

FIG. 1.



(*Note change of scale above* 20 *mm.*)

FIG. 2.



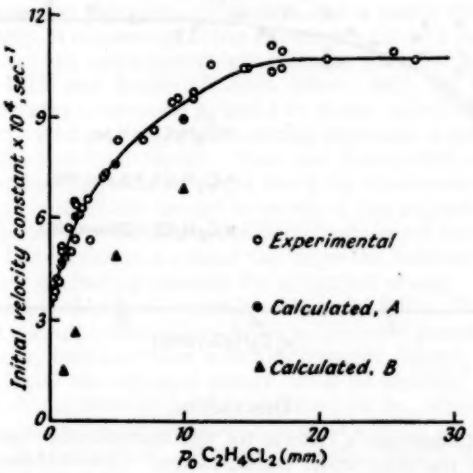
(*Note change of scale above* 30 *mm.*)

It is already known (Howlett, Thesis, London, 1948), that the reaction products, ethylene and hydrogen chloride, even when added in amounts equal to that of the decomposing substrate, have no effect upon the pyrolysis. It is established therefore that hydrogen chloride has no "chemical" catalytic influence upon the reaction. This has been confirmed in the present work, and it has also been shown (see Fig. 1) that the addition of about 10 mm. of hydrogen chloride restores the rate constant to the high-pressure value where the partial pressure of ethyl chloride is <8 mm. It was considered that with the present apparatus, the critical pressure was too low to allow a more quantitative study of the low-pressure region with ethyl chloride.

1 : 1-*Dichloroethane.*—The recalculated specific reaction rate (cf. Barton and Head, *loc. cit.*) for 1 : 1-dichloroethane pyrolysis in an unpacked reactor is constant over the range 20—200 mm. at $k = 10^{11\cdot65}\,e^{-49,300/RT}$ sec.$^{-1}$. The decomposition has been studied at 412°, 433°, and

449°. At higher pressures the mean rate constants were respectively 0·000157, 0·000488, and 0·00107 sec.$^{-1}$, in good agreement with those calculated from the equation above (0·000174, 0·000502, and 0·00107 sec.$^{-1}$). At each temperature studied, k begins to fall at pressures below 17—20 mm. This is illustrated in Figs. 1, 2, and 3. A notable feature of the kinetics below the critical pressure is that no fall in specific velocity is observed as reaction proceeds (with consequent lowering of the partial pressure of reactant). This implies that 1 mm. of vinyl chloride plus 1 mm. of hydrogen chloride are equal in efficiency for energy transfer to 1 mm. of dichloroethane (similar to the effect in azomethane decomposition noted by Ramsperger, *J. Amer. Chem. Soc.*, 1927, **44**, 1495). This fact is of considerable aid in determining the reaction order as a function of p_0. It was found that the decomposition remained virtually of first order down to 4 mm., below which the order began to rise noticeably and reached about 1·5 at 1 mm. The change over towards second-order kinetics has therefore been observed, but the pressure range over which accurate results could be obtained was insufficient to follow this effect to completion. As also shown in Fig. 2, additions of approx. 20 mm. of hydrogen chloride have no effect upon high-pressure results, but maintain the high-pressure constant below 17 mm. partial pressure of 1 : 1-dichloroethane.

FIG. 3.

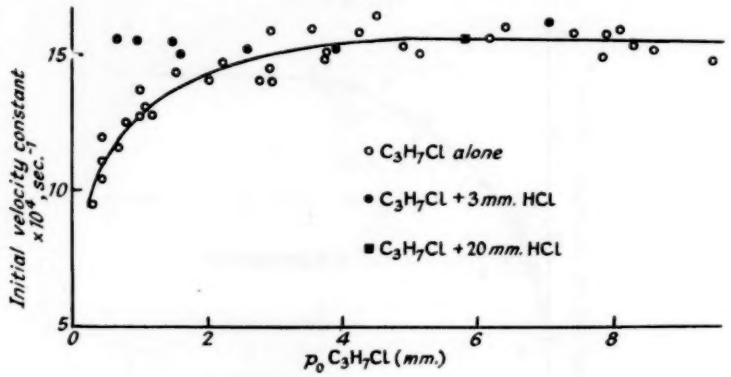


A number of co-decompositions of 1 : 1-dichloroethane (I) and 1 : 2-dichloroethane (II) have been carried out. Barton, Head, and Williams (*loc. cit.*) have discussed Ash and Brown's conclusions (" Records of Chemical Progress," 1948, p. 81) concerning the results of chlorine-atom attack upon the α- and β-hydrogen atoms in ethyl chloride, etc., in so far as they affect dehydrochlorination. The former authors have given good theoretical arguments for the correlation between structure and mode of decomposition given previously by Barton, Onyon, and Howlett (*Trans. Faraday Soc.*, 1949, **45**, 733). If this discussion is correct, (I) should be an inhibitor for the pyrolysis of (II), with little (if any) observable change in its own rate of decomposition. The co-decomposition has been studied at 446°, where the mean velocity constants for decomposition alone were found to be 0·00096 (0·00094) and 0·000334 (0·00034) sec.$^{-1}$ for (I) and (II), respectively. The figures in parentheses are those calculated from the published rate equations. In a number of experiments starting from 4 mm. of (I) + 20 mm. of (II), the observed rate of pressure increase was considerably less than the sum of the separate rates. Since inhibitors have no effect on the dehydrochlorination of (I), this proves that (I) is a fairly powerful inhibitor for the decomposition of (II). By assuming that (I) decomposed normally (see later) under these conditions, it is found that the rate of decomposition of (II) varies from about one-third of normal, with 4 mm. partial pressure of (I) present, to two-thirds of normal at 2 mm. of (I). These observations are facilitated because (I) reacts three times faster than even uninhibited (II). Attention was then turned to co-decompositions of 20 mm. of (I) + 4—9 mm. of (II). By assuming that, in these experiments, (II) decomposed at the maximally inhibited rate (Barton and Howlett, *J.*, 1949, 155), it was calculated that (I) decom-

posed at a mean rate constant of 0·00101 sec.$^{-1}$. There was no obvious correlation of this figure with the partial pressure of (II). Thus little (if any) decomposition is induced in (I) by the addition of chlorohydrocarbon radicals or chlorine atoms. These co-decompositions, therefore, amply confirm the predictions referred to above.

iso*Propyl chloride.* The investigation with this compound was similar to that with ethyl chloride. Barton and Head (*loc. cit.*) give $k = 10^{13\cdot4}\,e^{-50,500/RT}$ sec.$^{-1}$ for 2-chloropropane decomposition and show that the first-order constant is invariant over the initial pressure range 60—135 mm. Experiments have now been repeated at 406·6° (where Barton and Head find $k = 0{\cdot}00159$ sec.$^{-1}$), the variation of k with p_0 being studied. The results are plotted in Fig. 4. Very good agreement is obtained at higher pressures with the previous results, and the pressure range of applicability for their first-order constant is considerably extended. The velocity constant falls below $p_0 = 4$ mm. It has also been shown that the high-pressure rate constant could be restored, even when the partial pressure of *iso*propyl chloride was less than 3 mm., by the addition of 3 mm. of hydrogen chloride, which has no effect upon the high-pressure constant (cf. Fig. 4).

FIG. 4.



DISCUSSION

It is clear that Ramsperger's criteria for the unimolecular nature of a reaction are satisfied by the three reactions under consideration. Chloroethane, 1 : 1-dichloroethane, and 2-chloropropane pyrolyses all show a critical pressure region below which the velocity constant falls and the change over towards a second-order reaction has been established. We are therefore justified in using these reactions, particularly that of ethylidene dichloride, to examine the mathematical theory of unimolecular reactions. First, it is necessary to determine the number of degrees of freedom contributing towards the activation energy. Thus if $\frac{1}{2}n$ classical oscillators act as the energy reservoir, then the fraction of activated molecules at equilibrium is approximately

$$dN = \frac{e^{-[E+(\frac{1}{2}n-1)RT]/RT}([E+(\frac{1}{2}n-1)RT]/RT)^{(\frac{1}{2}n-1)}}{(\frac{1}{2}n-1)!}$$

and n may be calculated by using Figs. 1, 2, 3, and 4 (cf. Hinshelwood, "Kinetics of Chemical Change," Oxford, 1940, p. 81). The calculation of the experimental values of dN requires a knowledge of the effective molecular collisional diameters. These have not been determined, but Vogel (*Ann. Physik*, 1914, **43**, 1234) determined gaseous viscosities of methane, the chloromethanes, and ethane. From this, the variation of molecular diameter with chlorination of methane may be calculated, and by assuming increases of the same magnitude starting from ethane, the effective molecular diameters of ethyl chloride and 1 : 1-dichloroethane are estimated to be 5·5 and 6·0 Å, respectively. Similarly, from the viscosity data compiled for propane (Partington, "Advanced Treatise on Physical Chemistry," Longmans, 1949, p. 861) the molecular diameter of *iso*propyl chloride is set

at 6·0 Å. The use of these quantities in the equation above gives values of 13—14, 6—7, and 12 classical oscillators contributing towards the activation energy for the decomposition of these three compounds respectively. The first of these is the only one calling for comment. It is less than the possible classical limit (18), but by employing a quantised model the specific heat, $C_v°$, of ethyl chloride may be shown to be about 27 cal. degree^{-1} mole^{-1} at 730° K (Howlett, to be published). A small error in determining such a large value of n arises since $E \gg \frac{n}{2}RT$ (Fowler and Guggenheim, " Statistical Thermodynamics," Cambridge, 1949, p. 521). The inclusion of a second term in the expansion of the integral of the distribution law gives $\frac{1}{2}n = 13$. It seems, therefore, that with ethyl chloride the critical-pressure calculation of n gives an answer which is about the limit of possibility.

Several communications on unimolecular reactions have appeared in recent years (Eley, *Trans. Faraday Soc.*, 1943, **39**, 168; Evans and Rushbrooke, *ibid.*, 1945, **41**, 621; Barrer, *ibid.*, 1948, **44**, 399) in which rate-constant equations are given for the alternative mechanisms (the Polanyi–Hinshelwood or the Kassel–Rice–Ramsperger hypotheses). Evans and Rushbrooke, however, have concluded that a distinction between the possible slow stages of a unimolecular process is, in general, not a useful one, and since Barrer's method is tedious to apply, it has seemed better to examine the 1 : 1-dichloroethane decomposition by means of the very useful treatments given by Rice and Ramsperger (*J. Amer. Chem. Soc.*, 1927, **49**, 1617) and Kassel (*J. Phys. Chem.*, 1928, **32**, 225). Thus we shall employ the form of the curve connecting p_0 and k to obtain information about the way in which conversion of activated molecules into reacting molecules depends upon the magnitude and location of the molecular energy. Rice and Ramsperger (*loc. cit.*) have shown that a graph of $1/k$ against $1/p_0$ yields a straight line if the transformation probability for a molecule is independent both of the energy in excess of the activation energy and of its location within the molecule—in effect the simplified Hinshelwood treatment—but a curved plot if this is not so. The curvature is greater the larger the number of internal degrees of freedom which may be contributing towards the activation energy. Fig. 5 shows such a graph for the results obtained with 1 : 1-dichloroethane at 449°. The marked curvature, in a direction such that the rate is maintained better at the lower pressures than is accounted for on the simple theory, indicates that a localised-energy theory, with transformation probability dependent upon the excess of energy, must be applied. By extrapolation of Fig. 5 to $1/p_0 = 0$, a value of 0·00115 sec.$^{-1}$ is obtained for k_∞, whereas the experimental result is that k is approximately constant above 20 mm. at 0·00107 sec.$^{-1}$. This discrepancy is, however, not serious in kinetic work. We can also deduce from Fig. 5 that the Arrhenius activation energy should be pressure-variant below the critical pressure. In a localised energy case, the Arrhenius activation energy for the low-pressure second-order reaction should be $\frac{1}{2}(n - 3)RT$ cal. mole.$^{-1}$ less than that of the high-pressure first-order reaction. Unfortunately, the second-order region has only been approached, so we cannot use this limiting conclusion to obtain an independent measure of n, but a plot of the apparent activation energy (obtained by comparing results at 449° and 412°) against p_0 shows a definite fall at low pressures. This is shown in Fig. 6 and indicates that $\frac{1}{2}n > 4$, thus confirming the point made by Fig. 5.

In order to apply Rice and Ramsperger's treatment, it is necessary to integrate the equation

$$k = \frac{k_\infty}{kT\Gamma\left(\frac{n+1}{2}\right)} \int_0^\infty \frac{e^{-(\varepsilon-\varepsilon_0)/kT}\left(\frac{\varepsilon-\varepsilon_0}{kT}\right)^{(n-1)/2}}{1+\frac{\beta}{p}\frac{(\varepsilon-\varepsilon_0)^{(n-1)/2}}{\varepsilon^{(n-2)/2}}} \, d(\varepsilon-\varepsilon_0)$$

where $$\beta = k_\infty \frac{\Gamma\left(\frac{n}{2}\right)}{\Gamma\left(\frac{n+1}{2}\right)} \sqrt{\frac{m}{\pi}} \frac{1}{4s^2} e^{\varepsilon_0/kT}$$

deduced by them (their original symbolism is retained). This has been integrated graphically for 1 : 1-dichloroethane at 449° as shown in Fig. 7. The values inserted were : $\varepsilon_0 =$ 47,600 cal. mole^{-1} ($E_{exp.} - \boldsymbol{RT}$), $n = 13$, $s = 6 \times 10^{-8}$ cm., $k_\infty = 0{\cdot}00115$ sec.$^{-1}$; β, in units of mm. of Hg, is calculated to be $10^{10{\cdot}73}$. The outer curve of the graph corresponds to infinite pressure, succeeding curves being calculated for 10, 5, 2, and 1 mm., respectively. Qualitatively, it is seen that the greatest contribution to reaction comes from molecules having a moderate excess of energy (about 8 kcal. mole^{-1}, the equivalent of say 5 vibrational quanta/molecule) over the minimum necessary for activation, in agreement with Barrer's conclusion (*loc. cit.*) reached by use of the modified Polanyi–Hinshelwood hypothesis.

FIG. 6.

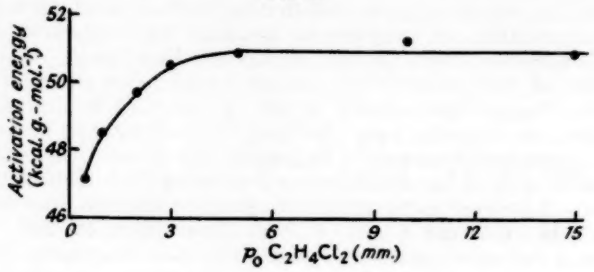


FIG. 5.

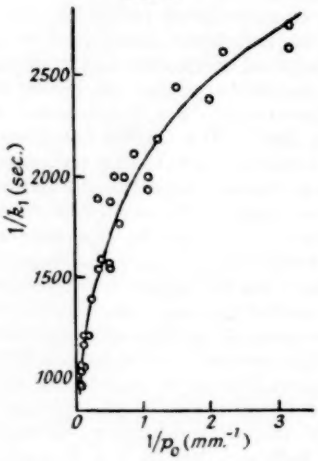
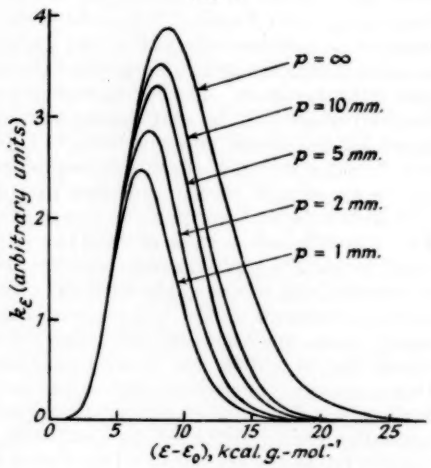


FIG. 7.



The areas under the curves are summed and plotted together with the experimental figures in Fig. 3 (there designated " Calculated, *A* "). As final evidence that the simple theory is inadequate to explain the results, Fig. 3 also shows the low pressure figures calculated (*B*) from this theory by using $k = k_\infty/(1 + \beta_1/p)$,

where $$\beta_1 = \frac{k_\infty \sqrt{m}(\boldsymbol{kT})^{(n-1)/2}\, e^{\varepsilon_0/\boldsymbol{kT}}\Gamma(\frac{1}{2}n)}{4\sqrt{\pi}\, s^2\, \varepsilon_0^{(n-2)/2}} = 6{\cdot}87 \text{ (mm. Hg units)}$$

Rice and Ramsperger's symbolism (*loc. cit.*) being used again. ε_0 is here 56,160 cal. mole^{-1} ($E_{exp.} + \frac{1}{2}(n-2)\boldsymbol{RT}$), s, n, and k_∞ being as before.

The more complex theory clearly gives the truer explanation of the facts, despite the fact that the theory strictly applies to the concentration of the energy into a single square term. It seems likely that in hydrogen chloride elimination reactions at least two square terms would be involved, but Kassel (" The Kinetics of Homogeneous Gas Reactions,"

Chem. Catalogue Co., 1932, p. 102) has stated that variation in the form of the k–p_0 curve is practically negligible in these two cases.

I wish to thank Professor E. E. Turner for his continuous interest and encouragement of the work described in this paper.

BEDFORD COLLEGE, LONDON, N.W.1. [*Received, April 25th*, 1952.]

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709. *The Decomposition of Aliphatic Diazo-compounds by Trimethyl Borate: The Preparation of Branched-chain Paraffins of High Molecular Weight.*

By G. D. BUCKLEY and N. H. RAY.

The decomposition of mixtures of diazomethane and higher aliphatic diazo-compounds by small amounts of trimethyl borate at 0° gives branched-chain paraffins of high molecular weight whose physical properties vary, with the number and length of the branches, from amorphous solids, through rubbers, to crystalline polymers resembling polythene but of very much higher melting point; their molecular weights are estimated to be of the order of 100,000. In contrast to the copper-catalysed decomposition of diazo-compounds, the presence of ether is not essential to the reaction, but the higher aliphatic diazo-compounds do not form polymers in the absence of diazomethane.

MEERWEIN (*Angew. Chem.*, 1948, **60**, *A*, 78) found that diazomethane was decomposed by catalytic amounts of a wide range of organic boron compounds, to give a polymer which he described as similar in appearance to filter-paper. Because it decomposed when heated, without melting, and was insoluble in all solvents tried, he concluded that it was a cross-linked polymer. This preparation has now been repeated, trimethyl borate being used as catalyst at 0°, and has been extended to a series of mixtures of higher aliphatic diazo-compounds with diazomethane; a wide variety of products has been obtained.

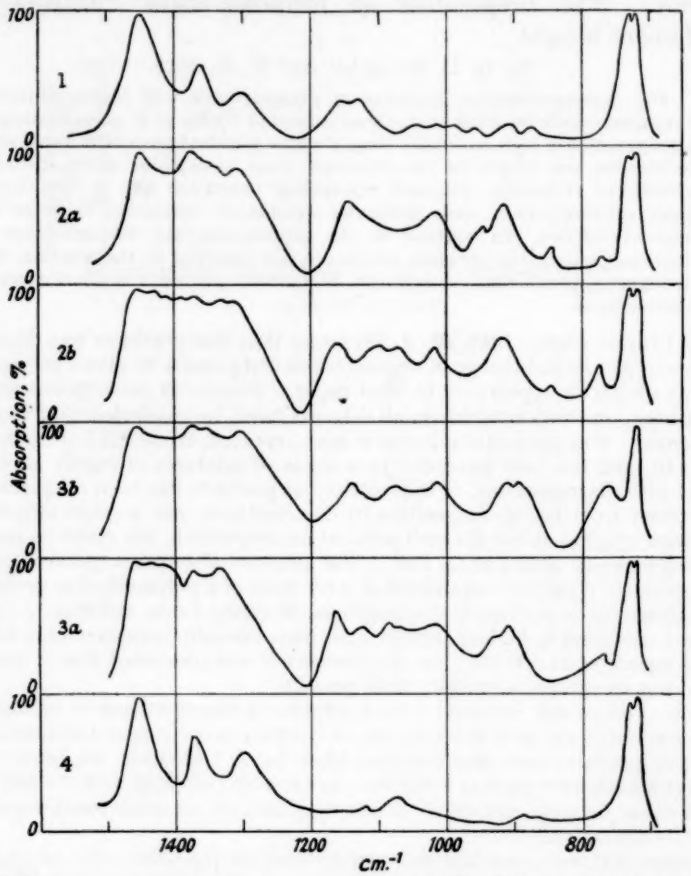
The product from the decomposition of diazomethane was a polymethylene of very high molecular weight; it did not melt without decomposition, but could be pressed into a film between rock-salt plates at *ca.* 180°. The infra-red absorption spectrum (Fig. 1) and the *X*-ray diffraction pattern were identical with those of a polymethylene prepared by the copper-catalysed decomposition of diazomethane (Buckley, Cross, and Ray, *J.*, 1950, 2714). The polymer dissolved in boiling tetralin, and from viscosity measurements its molecular weight was estimated at 200,000; on this evidence it was concluded that it was not cross-linked, and was essentially a straight-chain paraffin.

A similar product was obtained from a solution of diazomethane in benzene, showing that ether was not essential in this reaction, in contrast to the copper-catalysed decomposition. Similar products were also obtained when boron trifluoride, triphenyl borate, and tri*cyclo*hexyl borate were used as catalysts; as there did not appear to be any advantage in using another catalyst, trimethyl borate was used in all subsequent experiments on account of its ready availability.

Diazoethane did not give a high polymer by itself on treatment with trimethyl borate; the product was a tar, which was not investigated. In admixture with diazomethane, however, a paraffin of high molecular weight was obtained, which differed from the polymethylene formed from diazomethane alone in having greater solubility and lower melting point; its infra-red spectrum (Fig. 2, *a* and *b*) showed an absorption band at 1378 cm.$^{-1}$, indicative of methyl groups, and the intensity of this absorption was correlated with the proportion of diazoethane in the reaction mixture. The yield of the mixed polymers increased at first with increasing proportions of diazoethane, to a maximum at about 10 moles %, then decreased rapidly, approaching zero with more than 50 moles % of diazoethane in the mixture. From viscosity measurements, their molecular weights were estimated to lie between 100,000 and 200,000.

Similar mixed polymers were produced from mixtures of diazomethane and higher aliphatic diazo-compounds, up to 1-diazododecane, and the physical properties of these

materials depended on both the number and length of the branches introduced into the molecule. Crystallinity was decreased, and solubility increased, either by increasing the proportion of second component or by increasing its chain length: for example, a polymer from diazomethane and diazoethane containing 15 or more methyl groups per 100 carbon atoms was a rubber and soluble in cold chloroform; with diazohexane as second component these properties were apparent in a polymer containing 5 or more branches per 100 carbon atoms, and with diazododecane, only 3 branches per 100 carbon atoms were necessary to produce them.



1, *Polymethylene.*
2a, b, *Polymethylenes with methyl side chains.*
3a, b, *Polymethylenes with* n*-amyl side chains.*
4, *Polymethylene with* n*-undecyl side chains.*

The addition of a small proportion of 1 : 6-bisdiazohexane as second component to diazomethane resulted in the formation of a completely insoluble polymer; it was swollen by hot tetralin and, although it softened at 200°, it did not melt without decomposition.

Experimental

Preparation of Diazo-compounds.—Diazomethane, diazoethane, 1-diazohexane, and 1 : 6-bis-diazohexane were prepared from the corresponding nitrosoureas.

1-*Diazododecane.*—Dodecylurea (160 g.) and glacial acetic acid (640 c.c.) were warmed on a steam-bath until a clear solution was obtained, then cooled to 0° with vigorous stirring. A solution of sodium nitrite (200 g.) in water (340 c.c.) was added during 15 minutes, and stirring

continued for a further 15 minutes. An equal volume (*ca.* 1 l.) of ice-water was added, and the nitrosododecylurea collected at 0°.

Aqueous potassium hydroxide (250 c.c.; 40%), ethanol (500 c.c.), and ligroin (500 c.c.; b. p. 80—100°) were mixed and cooled to 0°, and the crude nitrosododecylurea (200 g.) was then added during 30 minutes with vigorous agitation. After a further 15 minutes' stirring at 0°, the upper layer (900 c.c.) was removed and filtered. This solution of 1-diazododecane was used without further purification in the experiments described below; for estimation and characterisation, one portion (30 c.c.) was added to benzoic acid (0·5 g.); nitrogen was evolved and the colour was discharged. The excess of acid was titrated with 0·1N-sodium hydroxide (15·0 c.c. required; whence concentration of diazododecane solution = 5·2 g./l.), and the solution extracted with ether. The ethereal extract was dried and evaporated, leaving an oily residue which was presumed to be impure *n*-dodecyl benzoate (0·3 g.) (Found: C, 67·5; H, 9·4. Calc. for $C_{19}H_{30}O_2$: C, 65·5; H, 9·66%).

Intrinsic Viscosities.—These were measured in tetralin solution at 75°, except where stated otherwise, by use of an Ubbelohde suspended level viscometer, modified by the addition of a large reservoir bulb to enable a series of dilutions to be made.

Branching and Crystallinity.—Infra-red absorption spectra were measured in the same instrument as was used in previous work (Buckley, Cross, and Ray, *loc. cit.*) and the amount of branching was determined by the method described by Cross, Richards, and Willis (*Discuss. Faraday Soc.*, 1950, **9**, 235). The intensity of the absorption band at 1304 cm.$^{-1}$ was used as a measure of the amorphous content; it was correlated with the amorphous : crystalline ratio as determined by *X*-ray diffraction.

General Procedure for Preparation of Polymers.—In a typical experiment, trimethyl borate (0·7 g.) was added to a solution of diazomethane (15 g.) and diazoethane (2 g.) in ether (710 c.c.) kept at 0°. Nitrogen was evolved slowly and a precipitate started to form in the solution. After 24 hours the solution was colourless; the precipitate was collected, washed with ether, and triturated with alcoholic approx. 2N-potassium hydroxide to remove boric acid and trimethyl borate. Finally it was washed with water, alcohol, and ether and dried. The product (5·3 g.) was a white, rubbery, fibrous mass, softening at 235° (in nitrogen), soluble in chloroform, benzene, and tetralin; it had d_4^{20} 0·899 and $[\eta]$ 3·3 (Found: C, 85·7; H, 14·3; B, nil. Calc. for $[CH_2]_x$: C, 85·7; H, 14·3%).

Infra-red absorption measurements gave 10·5 methyl groups per 100 carbon atoms and 22% crystallinity (Fig. 2*b*).

Polymethylene.—Diazomethane (13·7 g.) was decomposed by trimethyl borate (0·3 g.) in the manner described. The product (3·6 g.) was unchanged when heated in nitrogen up to 300°, above which it became progressively softer and darker, finally decomposing, as described by Meerwein (*loc. cit.*) to a brittle wax, m. p. about 110°. However, by heating it to 180° under pressure between rock-salt plates it was possible to obtain a thin, flexible, transparent film; its infra-red spectrum (Fig. 1) showed bands at 721 and 732 cm.$^{-1}$ characteristic of polymethylene, almost complete absence of methyl, and an amorphous content of 18%. Its *X*-ray diffraction pattern showed it to be a highly crystalline substance, and the interplanar spacings of the (110) and (200) reflections were identical with those of a polymethylene sample prepared by the copper-catalysed decomposition of diazomethane (Buckley, Cross, and Ray, *loc. cit.*). It dissolved slowly in tetralin at 160° and remained in solution at 100°; it had $[\eta]$ (at 100°) 5·4.

Polymethylenes with Side-chain Methyl Groups.—Mixtures of diazomethane and diazoethane in various proportions were decomposed at 0° as described, 0·01 mole of trimethyl borate being used per mole of total diazo-compound in each case. The following results were obtained:

Diazo-ethane, moles, %	Yield of polymer, % of theory	d_4^{20}	$[\eta]$	No. of Me groups per 100 C.	Crystal-linity, %	Remarks
3	66	0·925	3·62	2·5	64	Polythene-like, soluble in boiling toluene
6	71	0·931	2·85	2·8	57	
9	88	0·899	3·3	10·5	22	Flexible, soluble in hot benzene
10	99	0·888	3·5	11·5	26	
10	67	0·890	4·6	8·5	22	
12·5	47	0·906	—	7	33	
14·3	43	0·905	—	13	18	Rubbery
16·7	44	0·891	—	15	11	
20	40	0·878	—	16	6	
25	58	0·870	5·0	more	6	Soluble in cold $CHCl_3$
33·3	73	0·889	2·95	than	—	
50	9	0·910	2·87	20	—	

Polymethylenes with n-*Amyl Side Chains.*—Mixtures of diazomethane and 1-diazohexane in various proportions were decomposed at 0° with 0·01 mole of trimethyl borate per mole of total diazo-compound. The following results were obtained :

Diazohexane, moles, %	Yield of polymer, % of theory	d_4^{20}	$[\eta]$	No. of Me groups per 100 C.	Crystallinity, %	Remarks
6·25	50	0·911	1·9	3	38	Similar to polythene, soluble only in hot solvents
10·0	30	0·907	2·4	3	32	
12·5	60	0·905	7·4	5	38	Very rubber-like, soluble in cold $CHCl_3$
25	49	0·871	—	12	4	

The infra-red absorption spectra of the polymers made from 6·25 moles % and 25 moles % of diazohexane are shown in Figs. 3*a* and *b*.

Polymethylene with n-*Undecyl Side Chains.*—Trimethyl borate (0·5 g.) was added to a solution of diazomethane (6 g.) and 1-diazododecane (2·2 g.) in ether (700 c.c.). After 24 hours the precipitate was collected, washed, and dried. The product (2·0 g.) was a translucent rubbery solid, soluble in chloroform, benzene, and tetralin; it softened at 250°, and melted at 370° (in nitrogen), and had d_4^{20} 0·891, $[\eta]$ 6·95; its infra-red absorption spectrum showed 2·9 methyl groups per 100 carbon atoms and 22% crystallinity (Fig. 4).

Cross-linked Polymethylene.—Triphenyl borate (0·2 g.) was added to a solution of diazomethane (9·2 g.) and 1 : 6-bisdiazohexane (0·15 g.) in ether (1 l.). The solution was kept at 20° for 96 hours, after which a precipitate had formed. This was collected, washed, and dried; the product (2·4 g.) was a tough, flexible substance, d_4^{20} 0·921, which softened (without melting) at *ca.* 200° and decomposed at *ca.* 240°. Its infra-red absorption spectrum showed no methyl bands and about 50% crystallinity. It was insoluble in all solvents tried, though swollen by hot tetralin.

Decomposition of Diazomethane in Benzene.—Trimethyl borate (0·7 g.) was added to a solution of diazomethane (16·5 g.) in benzene (300 c.c.) at 20°. Nitrogen was evolved slowly, and a precipitate was formed in the solution. After 24 hours the solution was colourless, and the precipitate was collected, washed, and dried. The product (1·5 g.) was identical in properties and infra-red absorption spectrum with the polymethylene prepared in ether solution.

Attempted Decomposition of Diazoethane with Trimethyl Borate.—Trimethyl borate (1·0 g.) was added to a solution of diazoethane (19 g.) in ether (1 l.) at 0°. A very slow evolution of nitrogen occurred at first but did not continue. The solution was allowed to warm to 20° in 24 hours, after which it was still deep orange. More trimethyl borate (2·0 g.) was added; after 56 hours the solution was colourless but contained no precipitate; it was evaporated almost to dryness at 50° and finally heated at 100°/1 mm. until free from ether. The residue was washed with alkali to remove boric acid, dried, and distilled, giving a syrup, b. p. 60—120°/3 mm. (0·8 g.), and a tarry residue (1·3 g.).

The authors are indebted to Mr. L. H. Cross for the measurement and interpretation of the infra-red spectra.

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710. *Purpurogallin. Part X.* Further Studies on the Oxidation Products of Purpurogallin and Purpurogallincarboxylic Acid.*

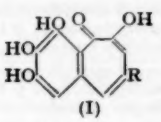
By W. D. Crow, R. D. Haworth, and P. R. Jefferies.

The methylation and decarboxylation of the acids (II; R = CO_2H) and (III; R = CO_2H), described in earlier papers, has been examined; the acid (III; R = CO_2H) has been converted by Curtius degradation into the β′-amine (III; R = NH_2) which with nitrous acid gave the corresponding β′-hydroxy-derivative. The acids (II; R = H and CO_2H) gave crimson anhydrides (X; R = H and CO_2H), and enol acetates and benzylidene derivatives are described. The anhydride constitution is supported by a study of the products obtained by reaction with (*a*) methyl alcohol and (*b*) ammonia, but the infra-red evidence suggests that the anhydride (X) exists entirely in an enolic form.

The yellow anhydride (XVII; R = O), now isolated in small yield from the oxidation of purpurogallin with hydrogen peroxide, resembles puberulonic acid in appearance and properties.

γ-Hydroxy-β-methyltropolone has been prepared by the action of potassium persulphate on β-methyltropolone, together with a smaller yield of the α- or α′-isomer.

In Part VII (*J.*, 1951, 1325) convenient methods for the preparation of purpurogallincarboxylic acid (I; R = CO_2H), β-carboxymethyltropolone-αβ′-dicarboxylic acid (II; R = CO_2H), and β-methyltropolone-β′-carboxylic acid (III; R = CO_2H) were described and these acids have now been investigated in more detail.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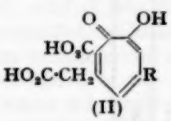
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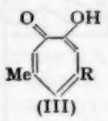
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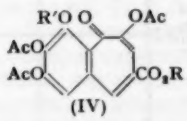

(IV)

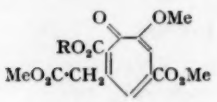
Perkin and Perkin (*J.*, 1903, **83**, 200; 1908, **93**, 1189) failed to prepare acetyl derivatives from purpurogallincarboxylic acid (I; R = CO_2H), but tri-, tetra-, and penta-acetates have now been obtained. The yellow triacetate probably (IV; R = R′ = H), was best prepared by the action of acetic anhydride and pyridine, and when warmed with acetic anhydride and potassium carbonate in acetone it was converted into a colourless tetra-acetate, probably (IV; R = H; R′ = Ac), which decomposed slowly in air to the yellow triacetate. Both these acetates were acidic, but a penta-acetate (IV; R = R′ = Ac), insoluble in sodium hydrogen carbonate solution, was obtained by the action of warm acetic anhydride on the tetra-acetate; the penta-acetate was readily hydrolysed to the tetra-acetate during attempted recrystallisation from aqueous alcohol.

β-Carboxymethyltropolone-αβ′-dicarboxylic acid (II; R = CO_2H) with methyl sulphate and sodium hydroxide yielded a yellow trimethyl ester, which gave a crimson ferric test and dissolved readily in aqueous sodium carbonate. Further methylation with ethereal diazomethane gave a neutral trimethyl ester methyl ether-A (V), m. p. 132—133°. The isomeric ether-B was obtained as an oil, and the constitution (V) assigned to the ether-A is based on analogy with the observations reported in Part IX (*J.*, 1951, 3427).

Methylation of β-methyltropolone-β′-carboxylic acid (III; R = CO_2H) with methyl sulphate and sodium hydroxide afforded the methyl ester (III; R = CO_2Me), m. p. 118—119°, which on further treatment with ethereal diazomethane gave a mixture of the methyl ethers-A (VI) and -B (VII), m. p. 117° and 81° respectively, but the constitutions of these ethers are again based on the experiments described in Part IX (*loc. cit*). It is noteworthy that the ether-B (VII), like tropolone methyl ether (Cook, Gibb, Raphael, and Somerville, *J.*, 1951, 503), was hydrated in the crystalline form, m. p. 81°, which liquefied on dehydration

* Part IX, *J.*, 1951, 3427.

and resolidified on exposure to air. β-Methyltropolone methyl ether-B (Part IX, *loc. cit.*) is crystalline in the anhydrous state, but in this form it is hygroscopic and liquefies by hydration in air.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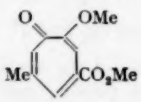
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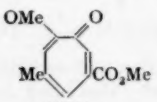
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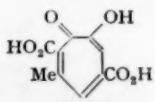
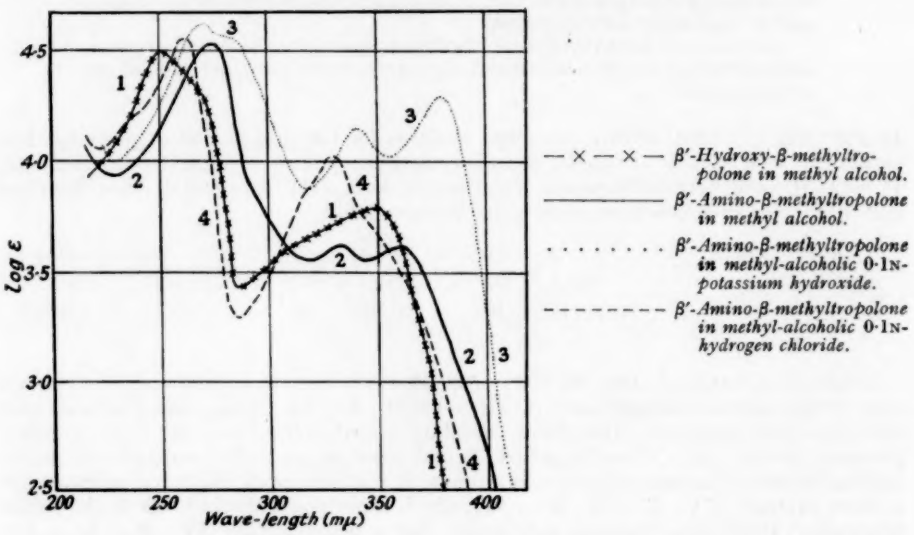

(VIII)

Heating β-carboxymethyltropolone-αβ′-dicarboxylic acid (II; R = CO_2H) in nitrobenzene afforded β-methyltropolone-αβ′-dicarboxylic acid (VIII) which melted at 245° (decomp.) with elimination of carbon dioxide and conversion into β-methyltropolone-β′-carboxylic acid (III; R = CO_2H). The dicarboxylic acid (VIII) with methyl sulphate and sodium hydroxide gave a dimethyl ester, and this or the acid (VIII) was converted into dimethyl β-methyltropolone-αβ′-dicarboxylate methyl ether-A, m. p. 137—138°, by ethereal diazomethane; the more soluble ether-B could not be crystallised.

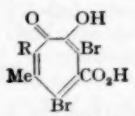


β-Methyltropolone-β′-carboxylic acid gave a dibromo-derivative, probably (IX; R = H), but even in the presence of excess of bromine tribromination could not be brought about. When, however, β-methyltropolone-αβ′-dicarboxylic acid (VIII) was treated with bromine in acetic acid solution, brominative decarboxylation took place and the tribromo-acid (IX; R = Br) was readily formed.

Methyl β-methyltropolone-β′-carboxylate (III; R = CO_2Me) reacted with hydrazine, and the product was converted by nitrous acid into a yellow amorphous azide (III; R = CON_3) from which the ethyl- and benzyl-urethanes (III; R = $NH{\cdot}CO_2Et$ and $NH{\cdot}CO_2{\cdot}CH_2Ph$ respectively) were prepared. The former was unaffected by acids or alkalis, and the benzylurethane gave a small amount of β′-amino-β-methyltropolone (III; R = NH_2) on hydrogenolysis. This amine was, however, more readily prepared by hydrolysis of the azide (III; R = CON_3) with a mixture of acetic and hydrochloric acid, and the ultra-violet absorption curves measured in neutral, acid, and alkaline solutions are shown in the Figure. The amine reacted with nitrous acid, nitrogen being eliminated and β′-hydroxy-β-methyltropolone (III; R = OH) produced. The ultra-violet absorption curve of the hydroxy-compound (see Figure) shows that the tropolone structure has been retained and that ring contraction to salicylic acid derivatives, encountered during the decomposition of

the α- and α′-amines (Part VIII, *J.*, 1951, 2067), is not observed in the case of the β-compound. Consequently the β-compound resembles the γ-derivative in this feature, although the failure to detect a diazonium salt at −20° from (III; R = NH_2) indicates a marked difference between the β- and the γ-position in other respects. This failure is probably connected with the fact that β-aminotropolone is the divinyl analogue of an acid amide and in this connection it is interesting that 2-amino-6-methyl*cyclo*heptatrienone (Part IX, *loc. cit.*) also fails to give a diazonium salt. This reaction will be discussed more fully in a later communication.

Although several reactions characteristic of phenols have failed with β-methyltropolone, the activity to certain electrophilic reagents led to an examination of the action of potassium persulphate. When the reaction was carried out under the conditions of Baker and Brown's experiments (*J.*, 1948, 2303), γ-hydroxy-β-methyltropolone, m. p. 232—233°, was obtained and identified by comparison with an authentic sample (Part IV, *J.*, 1951, 566); with acetic anhydride and pyridine it gave a diacetate, giving a negative ferric reaction and rapidly hydrolysed by alkali. An isomeric hydroxytropolone, m. p. 104—105°, was also obtained in smaller yields; it is probably α- or α′-hydroxy-β-methyltropolone and interaction of the α- or α′-hydroxyl group with the enolone system would account for the low melting point, the volatility, and the solubility properties of this compound.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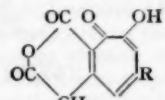
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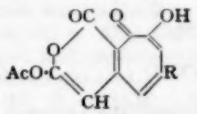
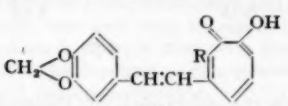

(XI)

When β-carboxymethyltropolone-αβ′-dicarboxylic acid (II; R = CO_2H) was warmed with concentrated sulphuric acid it was converted into a crimson compound, $C_{11}H_6O_7$, m. p. 249—251°, which is regarded as the anhydride (X; R = CO_2H). This formulation, which is consistent with the formation of an enol acetate (IX; R = CO_2H) is supported by the more detailed examination of the anhydride (X; R = H), which was prepared similarly by the action of warm sulphuric acid on β-carboxymethyltropolone-α-carboxylic acid (II; R = H). The anhydride (X; R = H) was readily converted into the corresponding acid (II; R = H) by boiling its aqueous solution, and Zerevitinoff estimation indicated the presence of two active hydrogen atoms, derived from the tropolone and enol-anhydride groupings respectively. The enol acetate (XI; R = H), which contained one active hydrogen atom on the basis of Zerevitinoff test and gave molecular-weight values in good agreement with the structure (XI; R = H), could be recovered from its solution in sodium hydrogen carbonate, although it was hydrolysed to the anhydride (X; R = H) by cold aqueous sodium hydroxide. The anhydride (X; R = H) condensed readily with aromatic aldehydes at 80° and yellow benzylidene, *o*-nitrobenzylidene, and piperonylidene (XII; R = CO_2H) derivatives have been obtained. Carbon dioxide is eliminated during the condensation and further decarboxylation to (XII; R = H) was effected when the piperonylidene derivative was heated to 230° in dibutyl phthalate. The enol acetate (XI; R = H) did not react with benzaldehyde.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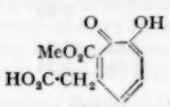
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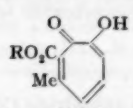
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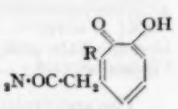
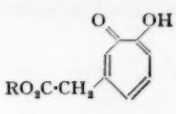

(XV)

When the anhydride (X; R = H) was warmed with methyl alcohol it afforded largely methyl β-carboxymethyltropolone-α-carboxylate (XIII), which was readily decarboxylated to methyl β-methyltropolone-α-carboxylate (XIV; R = Me), both descirbed in Part IV (*loc. cit.*). The acid (XIV; R = H) has now been obtained by partial decarboxylation of (II; R = H) in dibutyl phthalate or nitrobenzene at 170°. Rigid proof of the structure was not then available but it has now been obtained by alkali fusion of β-methyltropolone-

α-carboxylic acid (XIV; R = H): although a temperature of 320—340° was required, a 40% yield of 3-methylphthalic acid was obtained.

Treatment of the anhydride (X; R = H) with ammonia gave the amic acid, m. p. 167—169° (XV; R = CO_2H) which was decarboxylated in hot quinoline to the amide (XV; R = H). The amide was readily hydrolysed to β-carboxymethyltropolone (XVI; R = H), which was converted into β-methyltropolone on fusion and gave a methyl ester (XVI; R = Me) with methanolic hydrogen chloride. Thus ammonia and methyl alcohol attacked different seats of the anhydride (X; R = H) and, whilst this difference is not readily explained, it provides adequate proof of the anhydride structure.

Oxidation of purpurogallin (I; R = H) with hot alkaline hydrogen peroxide has been shown (Part IV, *loc. cit.*) to yield β-carboxymethyltropolone-α-carboxylic acid (II; R = H). Although it was not possible to oxidise this acid further without rupture of the tropolone nucleus, an examination of the residue from which the acid had been isolated yielded, in addition to oxalic acid, about 3% of the anhydride (XVII; R = O). This yellow anhydride gave a typical tropolone ferric test and formed an orange salt with sodium hydrogen carbonate; with hot sodium hydroxide it gave a pale yellow solution, back-titration of



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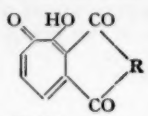

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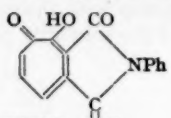

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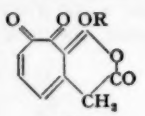

(XIX)

which showed the presence of three acid groups, but acidification yielded the anhydride (XVII; R = O), which was unaffected by hot alcohol either alone or in the presence of acids. The stability of the anhydride group is in agreement with the results obtained with puberulonic acid (Corbett, Hassall, Johnson, and Todd, *J.*, 1950, 1; Aulin-Erdtman, *Acta. Chem. Scand.*, 1951, **5**, 301). The anhydride was decarboxylated in water at 180°, affording tropolone-β-carboxylic acid. The position of the remaining carbon atom was established by fusion of the anhydride with sodium hydroxide at 180°, which yielded hemimellitic acid. Corbett *et al.* (*loc. cit.*) describe the preparation of an *o*-phenylenediamine condensation product of puberulonic acid, but although the anhydride (XVII; R = O) reacted rapidly with *o*-phenylenediamine the basic product was probably an *o*-amino-*N*-phenylimide. The anhydride (XVII; R = O) gave a yellow *N*-phenylimide (XVII; R = NPh) with aniline in acetic acid, but when this or the anhydride was heated with a large excess of aniline a scarlet compound, m. p. 281—283°, containing two aniline residues and possibly (XVIII) was obtained. Both the *N*-phenylimide and the aniline derivative gave tropolone colour tests, are virtually non-basic and very weak acids, on hydrolysis slowly regenerate the anhydride.

We are very much indebted to Drs. R. N. Haszeldine and A. W. Johnson for the infrared absorption spectra which were measured in paraffin mull. The following strong bands were observed in the 6-μ region.

Anhydride of	Bands (μ)					
Tropolone-αβ-dicarboxylic acid (XVII)	5·47	5·61	6·1	6·15		6·34
β-Carboxymethyltropolone-α-carboxylic acid (X; R = H)		5·89		6·15		6·53
Homophthalic acid	5·63	5·7			6·23	
Glutaconic acid	5·59	5·73				

The spectrum of the anhydride (XVII) is in full accord with the structure; the doublet at 6·1 and 6·15 μ, and the 6·34-μ band, are assigned to the basic tropolone structure (Koch, *J.*, 1951, 512; Scott and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 240), and the absorptions at 5·47 and 5·61 μ are assigned to the anhydride doublet, in close agreement with the values 5·46 and 5·65 μ found in puberulonic acid (Johnson, Sheppard, and Todd, *J.*, 1951, 1139; Aulin-Erdtman and Theorell, *Acta Chem. Scand.*, 1950, **4**, 1490). On the other hand, the spectrum of β-carboxymethyltropolone-α-carboxylic anhydride is inconsistent with structure (X; R = H), and the anhydride doublet, observed in homophthalic and

glutaconic anhydrides at 5·63 and 5·7 μ and 5·59 and 5·73 μ respectively, is absent. This abnormal result is probably best explained by postulating an enolic structure for the tropolone anhydride. In this connection it is noted that Nozoe *et al.* (*Proc. Jap. Acad.*, 1952, **28**, 32), in a communication which became available when this paper was in manuscript form, suggested a structure such as (XIX; R = Ac) for the enol acetate (XI; R = H) in order to account for the pronounced colour of this compound.

Experimental

Acetylation of Purpurogallincarboxylic Acid.—The acid (I; R = CO_2H) (1 g.) was warmed for 30 minutes with acetic anhydride (2 c.c.) containing a few drops of pyridine; the *triacetate* (IV; R = R′ = H), isolated by dilution with water and extraction with ether, separated from toluene containing a little acetone in yellow needles (0·6 g.), m. p. 219—220° (Found: Ac, 33·1. $C_{18}H_{14}C_{10}$ requires Ac, 33·1%), soluble in sodium hydrogen carbonate. The triacetate (0·5g.) was refluxed for 30 minutes in acetone (25 c.c.) with acetic anhydride (2 c.c.) and anhydrous potassium carbonate (5 g.). The solid was collected, washed with acetone, and decomposed with dilute hydrochloric acid; the *tetra-acetate* (IV; R = H, R′ = Ac), isolated with ether and crystallised from acetic acid, formed colourless needles (0·35 g.), m. p. 207—208° (Found: C, 55·5; H, 3·9; Ac, 41·2. $C_{20}H_{16}O_{11}$ requires C, 55·6; H, 3·7; Ac, 39·8%). Crystallisation from acetic anhydride gave the *penta-acetate* (IV; R = R′ = Ac) as colourless prisms, m. p. 156—157° (Found: Ac, 45·2. $C_{22}H_{18}O_{12}$ requires Ac, 45·3%), which was insoluble in sodium hydrogen carbonate solution and decomposed to the tetra-acetate, m. p. 207—208°, during attempted recrystallisation from aqueous alcohol. The tri-, tetra-, and penta-acetate were hydrolysed by methyl-alcohlic hydrochloric acid to purpurogallincarboxylic acid.

Methylation of β-Carboxymethyltropolone-αβ′-dicarboxylic Acid (II; R = CO_2H).—The acid (1 g.) in 10% sodium hydroxide (5 c.c.) was shaken with methyl sulphate (1·4 c.c.), for 15 hours. The solid was collected and crystallised from carbon tetrachloride; the *trimethyl* ester (0·6 g.) was obtained as yellow needles, m. p. 161—162° (Found: C, 54·3; H, 4·5. $C_{14}H_{14}O_8$ requires C, 54·2; H, 4·5%), which gave a crimson ferric test and dissolved in sodium carbonate solution.

Further treatment of the trimethyl ester (0·5 g.) with a small excess of ethereal diazomethane yielded a yellow gum, insoluble in sodium hydroxide and showing no ferric reaction. Trituration with ether gave the *trimethyl* ester *methyl ether-A* (V) as a pale yellow solid (0·3 g.), crystallising from benzene–light petroluem (b. p. 60—80°) in yellow prisms. m. p. 132—133° (Found: C, 56·0; H, 5·1. $C_{15}H_{14}O_8$ requires C, 55·6; H, 5·0%). The ether-soluble fraction could not be induced to crystallise.

Methylation of β-Methyltropolone-β′-carboxylic Acid (III; R = CO_2H).—Treatment of the acid (III; R = CO_2H) with methyl sulphate in the usual way gave the *methyl* ester (III; R = CO_2Me) which crystallised from aqueous acetone in yellow needles, m. p. 118—119° (Found: C, 61·7; H, 5·3. $C_{10}H_{10}O_4$ requires C, 61·8; H, 5·2%), soluble in sodium carbonate solution and giving a red ferric test.

Further methylation with excess of ethereal diazomethane gave an oil which was repeatedly extracted with boiling light petroleum (b. p. 60—80°); the combined extracts were evaporated, and the residual oil crystallised from light petroleum (b. p. 45—60°). The less soluble *methyl β-methyltropolone-β′-carboxylate methyl ether-A* (VI) was obtained as pale yellow needles, m. p. 117—118° (Found: C, 63·4; H, 6·1. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%), and the more soluble *ether-B* (VII) as pale yellow hydrated needles, m. p. 80—81° (Found: C, 61·7; H, 5·9; H_2O, 3·1. $C_{11}H_{12}O_4,\frac{1}{3}H_2O$ requires C, 61·7; H, 6·0; H_2O, 2·9%), which liquefied when dried over phosphoric oxide and resolidified on exposure to the air. Both ethers gave a negative ferric test and were insoluble in dilute sodium hydroxide solution although with cold 10% sodium hydroxide they were gradually hydrolysed to the ester (III; R = CO_2Me), m. p. 118—119°; both ethers were converted into the acid (III; R = CO_2H), m. p. 222—223°, by warm 10% sodium hydroxide.

β-Methyltropolone-αβ′-dicarboxylic Acid (VIII).—The acid (II; R = CO_2H) (1 g.) was heated in nitrobenzene (10 c.c.) at 180° for 5 minutes and finally boiled for 1 minute. The product was diluted with light petroleum (b. p. 60—80°) (20 c.c.), filtered, recovered by evaporation under reduced pressure, and crystallised from water (charcoal). *β-Methyltropolone-αβ′-dicarboxylic acid* was obtained as yellow plates (0·72 g.), m. p. 247—248° (decomp.) (Found: C, 53·4; H, 3·8. $C_{10}H_8O_6$ requires C, 53·6; H, 3·6%), readily soluble in sodium hydrogen carbonate solution, giving a red ferric test, and decarboxylated to β-methyltropolone-β′-carboxylic acid (III; R = CO_2H), m. p. 222—223°, at 250°. The *dimethyl* ester, prepared from (VIII)

(0·5 g.), 20% aqueous sodium hydroxide (1·25 c.c.), and methyl sulphate (0·6 c.c.), separated from carbon tetrachloride in pale yellow needles (0·4 g.), m. p. 106—107° (Found: C, 56·8; H, 4·7. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%), which dissolved slowly in aqueous sodium hydrogen carbonate and gave a red ferric test. *Dimethyl β-methyltropolone-αβ′-dicarboxylate methyl ether-A*, prepared by the action of ethereal diazomethane on the acid (VIII) or its dimethyl ester, crystallised from benzene–light petroleum (b. p. 60—80°) in yellow prisms, m. p. 137—138° (Found: C, 58·6; H, 5·4. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%), which were alkali-insoluble and no longer gave a ferric test. The mother-liquors yielded a clear gum which could not be crystallised.

Bromination of β-Methyltropolone-β-carboxylic Acid (III; R = CO_2H).—The acid (0·5 g.) in 90% acetic acid (5 c.c.) was treated with bromine (0·6 c.c.), and after 24 hours at room temperature the mixture was diluted with water and the *dibromo-acid* (IX; R = H) was collected and crystallised from acetic acid; yellow needles (0·5 g.), m. p. 214—215° (decomp.) (Found: C, 32·3; H, 1·9; Br. 46·7. $C_9H_6O_4Br_2$ requires C, 32·0; H, 1·8; Br. 47·3%), were obtained, which were unaffected by boiling with 20% sodium hydroxide solution and gave a red ferric test.

Bromination of β-Methyltropolone-αβ′-dicarboxylic Acid (VIII).—This, when carried out as described above, yielded the *tribromo-acid* (IX; R = Br), yellow plates (from acetic acid), m. p. 222—223° (decomp.) (Found: C, 26·5; H, 1·4; Br, 57·6. $C_9H_5O_4Br_3$ requires C, 25·9; H, 1·2; Br, 57·3%), which gave a red ferric test but was unaffected by boiling 20% sodium hydroxide solution.

β-Methyltropolone-β′-carboxylic Azide (III; R = CON_3).—Methyl β-methyltropolone-β′-carboxylate (III; R = CO_2Me) (2·0 g.) was heated at 100° for 3 minutes with 90% hydrazine solution (1 c.c.), then allowed to cool, and the yellow water-soluble product (1·9 g.), m. p. 171—172° (decomp.), precipitated by the addition of alcohol (35 c.c.), collected, and dissolved in 5% hydrochloric acid (20 c.c.). Addition of 7·5% sodium nitrite (10 c.c.) at −10° then precipitated the *azide* (III; R = CON_3), which was collected, washed, and dried in a vacuum. The amorphous product (1·35 g.), m. p. 119—120° (decomp.) (Found: N, 21·0. $C_9H_7O_3N_3$ requires N, 20·4%), gave a red ferric test.

β-Methyltropolone-β′-carboxylic acid N-ethylurethane (III; R = NH·CO_2Et), prepared by evaporation of a solution of the azide (III; R = CON_3) (0·5 g.) in ethyl alcohol (20 c.c.), was purified first by sublimation and then by crystallisation from water; it separated in colourless needles (0·45 g.), m. p. 174—175° (Found: C, 59·5; H, 5·6; N, 6·5. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·9; N, 6·3%), insoluble in dilute acids, soluble in sodium hydroxide solution, and giving a red ferric test.

β-Methyltropolone-β′-carboxylic acid N-benzylurethane (III; R = NH·CO_2·CH_2Ph), prepared by heating the azide (0·5 g.) with benzyl alcohol (0·5 c.c.) for a few minutes at 150°, crystallised from ethyl alcohol in colourless needles (0·6 g.), m. p. 185—186° (Found: C, 67·6; H, 5·6. $C_{16}H_{15}O_4N$ requires C, 67·4; H, 5·3%).

β′-Amino-β-methyltropolone (III; R = NH_2).—(*a*) This was prepared in small yield by shaking the above *N*-benzylurethane in alcohol with 10% palladium–charcoal and hydrogen for 1 hour.

(*b*) It was obtained in better yield by refluxing for 2 hours a solution of the azide (III; R = CON_3) (1 g.) in acetic acid (10 c.c.) containing 10N-hydrochloric acid (2 c.c.); the acetic acid was removed in steam, and the residual solution neutralised by careful addition of sodium hydrogen carbonate and continuously extracted with ether. The ether was removed and the *amine* (III; R = NH_2) crystallised from water, forming cream-coloured needles (0·48 g.), m. p. 199—200° (Found: C. 63·5; H, 6·3; N, 9·3. $C_8H_9O_2N$ requires C, 63·6; H, 6·0; N, 9·3%), readily soluble in dilute hydrochloric acid or aqueous sodium hydroxide and giving a red ferric test.

β′-Hydroxy-β-methyltropolone (III; R = OH).—The amine (III; R = NH_2) (0·3 g.) in 5% sulphuric acid (20 c.c.) was treated with a solution of sodium nitrite (0·15 g.) in water (5 c.c.) at −20°. Nitrogen was evolved and the solution, which did not couple with an alkaline solution of β-naphthol, was treated with urea and boiled for a few minutes; the cooled solution extracted continuously with ether. The concentrated extract was sublimed at 0·1 mm., and the *product* (III; R = OH) crystallised from alcohol, forming straw-coloured prisms (0·19 g.), m. p. 241—242° (Found: C, 63·0; H, 5·5. $C_8H_8O_3$ requires C, 63·2; H, 5·3%), which gave a red ferric test.

Oxidation of β-Methyltropolone with Potassium Persulphate.—A solution of potassium persulphate (4 g.) in water (130 c.c.) was added with stirring during 4 hours to an ice-cooled suspension of the sodium salt obtained by adding β-methyltropolone (2 g.) to 10% sodium hydroxide solution (40 c.c.). After 12 hours at 0°, the solution was acidified to Congo-red, and extracted

with ether which removed unchanged β-methyltropolone (0·55 g.) and a brown tar. The aqueous portion was acidified further with concentrated hydrochloric acid (10 c.c.), heated at 100° for 1 hour, and continuously extracted with ether. The product, triturated with a little ether (A), solidified. Sublimation at 190°/0·05 mm. and crystallisation from alcohol gave γ-hydroxy-β-methyltropolone as a mixture of stout and elongated prisms (0·44 g.), m. p. 232—233° (decomp.) (Found: C, 63·5; H, 5·6. Calc. for $C_8H_8O_3$, C, 63·2; H, 5·3%), identical with the material described in Part IV (*loc. cit.*). The *diacetate*, prepared by boiling acetic anhydride and a drop of pyridine and isolated with chloroform, sublimed at 120—130°/0·01 mm. and crystallised from carbon tetrachloride in colourless prisms, m. p. 129—130° (Found: C, 61·3; H, 4·9; Ac, 35·9. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1; Ac, 36·4%), giving a negative ferric test. Evaporation of the ethereal washings (A) gave an oil, which was extracted with hot carbon tetrachloride (2 × 30 c.c.); evaporation of this extract gave a crystalline residue of α(or α′-)-*hydroxy*-β-*methyltropolone* which sublimed at 100°/12 mm., and crystallised from carbon tetrachloride in cream-coloured needles (0·1 g.), m. p. 103—105° [Found: C, 62·9; H, 5·3% *M* (Rast), 165. $C_8H_8O_3$ requires C, 63·2; H, 5·3%; M, 152·1], readily soluble in dilute aqueous sodium hydroxide and giving a green ferric test.

Anhydride (X; R = CO_2H) *of* β-*Carboxymethyltropolone*-αβ′-*dicarboxylic Acid*.—The acid (II; R = CO_2H) (1 g.) was warmed at 60° for a few minutes with concentrated sulphuric acid (5 c.c.) and after 5 minutes the mixture was poured into water (200 c.c.). The crimson *anhydride* (X; R = CO_2H) was collected and separated from dioxan in lustrous plates (0·7 g.), m. p. 249—251° (decomp.) (rapid heating) (Found: C, 52·8; H, 2·6. $C_{11}H_6O_7$ requires C, 52·6; H, 2·4%), readily soluble in aqueous sodium hydrogen carbonate, giving an olive-green ferric test, and hydrolysed to the tricarboxylic acid (II; R = R′ = CO_2H) by boiling water, hydrochloric acid, or sodium hydroxide. The enol *acetate* (XI; R = CO_2H), prepared by heating the acid (II; R = CO_2H) (0·5 g.) with acetic anhydride (2—3 c.c.) under reflux for 10 minutes, crystallised from toluene in dark red needles (0·37 g.), m. p. 210—212° (decomp.) (Found: Ac, 14·2. $C_{13}H_8O_8$ requires Ac, 13·6%), soluble in cold sodium hydrogen carbonate solution from which it was recovered by acidification. With cold 10% sodium hydroxide solution it gave the anhydride (X; R = CO_2H), m. p. 249—251° (decomp.).

Anhydride (X; R = H) *of* β-*Carboxymethyltropolone*-α-*carboxylic Acid*.—Prepared similarly from the acid (II; R = H), this *anhydride* sublimed at 100°/0·01 mm. and crystallised from dioxan or anisole in dark red prisms, m. p. 205—208° (decomp.) (Found: C, 58·3; H, 3·3%; active H, 1·9, 2·0 atoms. $C_{10}H_6O_5$ requires C, 58·3; H, 2·9%; active H, 2·0 atoms). Light absorption in dioxan showed maxima at 275, 315, and 475 mμ (log ε 4·0, 4·0, 4·21, and 3·12 respectively). The colour of a chloroform solution was intensified by addition of ferric chloride. The *enol* acetate (XI; R = H), obtained from (II; R = H) by boiling acetic anhydride, crystallised from toluene or acetic acid as dark red monoclinic crystals, m. p. 192—193° (decomp.) [Found; C, 58·4; H, 3·3; acetyl, 17·0%; active H, 1·1, 1·1 atom; *M* (ebullioscopic in chloroform), 230, 235. $C_{12}H_8O_6$ requires C, 58·1; H, 3·3; acetyl, 17·3%; active H, 1·0 atom; M, 248]. Light absorption in dioxan showed maxima at 290, 350, 365, and 470 mμ (log ε 4·20, 4·21, 4·15, and 2·99 respectively). The enol acetate (XI; R = H) dissolved with effervescence in sodium hydrogen carbonate solution and gave a positive test, and hydrolysis to the anhydride (X; R = H) took place in sodium hydroxide solution. No reaction took place when the enol acetate was heated with benzaldehyde at 160°.

β-3 : 4-*Methylenedioxystyryltropolone*-α-*carboxylic Acid* (XII; R = CO_2H).—The anhydride (X; R = H) (0·4 g.) was warmed at 100° with piperonaldehyde (2 g.); carbon dioxide was evolved. The excess of aldehyde was removed in benzene and the residual *derivative* crystallised from dioxan as yellow needles (0·55 g.), m. p. 212—214° (decomp.) (Found: C, 64·9; H, 4·1. $C_{17}H_{12}O_6$ requires C, 65·4; H, 3·9%), which effervesced and formed a sparingly soluble salt with sodium hydrogen carbonate solution and gave a red ferric test.

The *styryl* derivative, prepared similarly, separated from ethyl acetate or acetic acid in yellow prisms, m. p. 167—169° (decomp.) (Found: C, 71·7; H, 4·5. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%).

The 2-*nitrostyryl* derivative crystallised from acetic acid–dioxan in brown-yellow needles, m. p. 203—205° (decomp.) (Found: N, 4·4. $C_{16}H_{11}O_6N$ requires N, 4·5%).

β-3 : 4-*Methylenedioxystyryltropolone* (XII; R = H).—The above methylenedioxystyryl derivative (XII; R = CO_2H) (0·5 g.) was heated at 220—230° with a little copper bronze in dibutyl phthalate (4 c.c.) until gas evolution ceased. 3 : 4-*Methylenedioxystyryltropolone* (0·3 g.), precipitated with light petroleum (b.p. 60—80°) (10 c.c.), sublimed at 200—210°/0·5 mm., and crystallised from benzene as yellow needles, m. p. 191—192° (Found: C, 71·7; H, 4·4.

$C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%), which gave an insoluble sodium salt with sodium hydroxide solution.

Methyl β-Carboxymethyltropolone-α-carboxylate (XIII).—The anhydride (X; R = H) (0·22 g.) was boiled with methyl alcohol (10 c.c.) and dioxan (5 c.c.) for 1 hour. The residue, obtained by evaporation of the colourless solution, crystallised from methyl alcohol yielding methyl β-carboxymethyltropolone-α-carboxylate (XIII), m. p. 179—180° (decomp.), identical with a sample described in Part IV (*loc. cit.*). Identity was confirmed by decarboxylation to methyl β-methyltropolone-α-carboxylate (XIV; R = Me), m. p. 122—123° (Part IV, *loc. cit.*, and below).

β-Methyltropolone-α-carboxylic Acid (XIV; R = H) [with J. D. Hobson].—In addition to the method outlined above and the methods described in Part IV (*loc. cit.*), this acid may be prepared by partial decarboxylation of β-carboxymethyltropolone-α-carboxylic acid (II; R = H). This acid (10 g.) was heated with nitrobenzene or dibutyl phthalate (50 c.c.) at 170° until evolution of gas ceased. The cooled solution was diluted with ether, filtered, and extracted with sodium hydrogen carbonate solution. Acidification of the extract yielded β-methyltropolone-α-carboxylic acid (XIV; R = H) which separated from hot water (charcoal) in colourless needles (5 g.), m. p. 190—191° (decomp.) (Found: C, 60·3; H, 4·8. Calc. for $C_9H_8O_4$: C, 60·0; H, 4·5%). Methylation with methyl sulphate and sodium hydroxide gave methyl β-methyltropolone-α-carboxylate (XIV; R = Me), m. p. 122—123° (Part IV, *loc. cit.*, and above).

Alkaline Fusion of β-Methyltropolone-α-carboxylic Acid.—The acid (XIV; R = H) (1 g.) was fused with sodium hydroxide (7 g.) at 330—340° for 5 minutes. The product was dissolved in water, acidified, boiled with charcoal, and filtered whilst hot. The cooled filtrate was extracted with ether (4 × 50 c.c.), and the solvent evaporated. Impurities were removed from the crude product with hot *cyclo*hexane, and the residue, crystallised from 2N-hydrochloric acid, had m. p. 152—153°, undepressed by admixture with 3-methylphthalic acid (Jurgens, *Ber.*, 1907, **40**, 4409; Müller, *Ber.*, 1909, **42**, 430); sublimation gave the anhydride, m. p. 116—117° (Found: C, 66·8; H, 4·0. Calc. for $C_9H_6O_3$: C, 66·7; H, 3·7%) alone or mixed with 3-methylphthalic anhydride.

β-Carbamylmethyltropolone-α-carboxylic Acid (XV; R = CO_2H).—The anhydride (X; R = H) (0·15 g.) was shaken with ammonia (1 c.c.; *d* 0·88). When the colour had faded excess of ammonia was removed on the water-bath and the solution acidified to Congo-red. The *amic acid* (XV; R = CO_2H) (0·13 g.) which separated crystallised from water in cream-coloured prisms, m. p. 167—168° (decomp.) (Found: C, 53·8; H, 4·3; N, 6·3. $C_{10}H_9O_5N$ requires C, 53·8; H, 4·1; N, 6·2%), which dissolved in sodium hydrogen carbonate solution and gave a green ferric test.

β-Carbamylmethyltropolone (XV; R = H).—The amic acid (XV; R = CO_2H) (1 g.) was heated at 130° in quinoline (2 c.c.) until gas evolution ceased (10 minutes). The cooled solution deposited crystals (0·5 g.) of the *amide* which were washed with dilute acid, sublimed at 200—210°/0·01 mm., and crystallised from water, forming cream-coloured prisms, m. p. 216—218° (Found: C, 59·9; H, 5·0; N, 7·7. $C_9H_9O_3N$ requires C, 60·3; H, 5·1; N, 7·85%), insoluble in aqueous sodium hydrogen carbonate and giving a red ferric test.

β-Carboxymethyltropolone (XVI; R = H).—The amide (XV; R = H) (0·4 g.) was heated under reflux with 2N-sodium hydroxide 10 c.c.) until evolution of ammonia ceased (30 minutes). Extraction of the acidified solution with ether gave the *acid* (XVI; R = H), which crystallised from alcohol or water in needles, m. p. 156—158° (decomp.) (Found: C, 59·9; H, 4·4. $C_9H_8O_4$ requires C, 60·0; H, 4·5%), soluble in sodium hydrogen carbonate, giving a green ferric test and decarboxylated to β-methyltropolone when heated above its m. p. The *methyl* ester, prepared with methyl-alcoholic hydrogen chloride, crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 67—68° (Found: C, 61·3; H, 5·5. $C_{10}H_{10}O_4$ requires C, 61·8; H, 5·2%), giving a green ferric reaction.

Tropolone-αβ-dicarboxylic Anhydride (XVII; R = O).—The ethereal liquors, from which β-carboxymethyltropolone-α-carboxylic acid had been isolated, from the oxidation of purpurogallin (120 g.) (Part IV, *loc. cit.*) were evaporated and the dark red residual oil was taken up in acetone–ether (1 : 3; 400 c.c.). The solid which gradually separated was periodically removed, and the solution was repeatedly made up to volume by addition of ether. The early crops consisted mainly of β-carboxymethyltropolone-α-carboxylic acid, but the last crops were mainly oxalic acid and intermediate fractions were mixtures containing the *anhydride* (XVII; R = O), which was isolated by washing with a little hot water and purified by sublimation and crystallisation from acetic acid or diethyl malonate; yellow plates (3·5 g.), m. p. 251—253° (Found: C, 55·9; H, 2·5%; equiv., 63·0. $C_9H_4O_5$ requires C, 56·3; H, 2·1%; equiv., 64·0), were

obtained. The anhydride gave a red green ferric test, and a sparingly soluble orange salt with aqueous sodium hydrogen carbonate, but it was unaffected by boiling ethyl alcohol.

Tropolone-β-carboxylic Acid.—The anhydride (0·4 g.) was suspended in water (5 c.c.) and heated at 170—180° for 30 minutes. The cooled solution deposited tropolone-β-carboxylic acid (0·2 g.) which crystallised from dioxan in solvated prisms, m. p. (dioxan-free) 217° alone or mixed with a sample prepared as described in Part IV (*loc. cit.*). The *methyl* ester prepared (with J. D. Hobson) by methyl-alcoholic hydrogen chloride, crystallised from benzene in pale cream-coloured plates, m. p. 117—118° (Found: C, 60·3; H, 4·5. $C_9H_8O_4$ requires C, 60·0; H, 4·5%), which gave a red ferric test and slowly dissolved to a yellow solution in sodium hydrogen carbonate solution.

Methylation of tropolone-β-carboxylic acid with ethereal diazomethane gave a brown gum which gave a negative ferric test.

Alkaline Fusion of Tropolone-αβ-dicarboxylic Anhydride.—The anhydride (XVII; R = O) (0·3 g.), fused with sodium hydroxide (3 g.) at 170—180° for 3 minutes, gave an almost colourless melt, which was dissolved in water, acidified, and extracted continuously with ether. The product, after three crystallisations from dilute hydrochloric acid (1 : 4), had m. p. 195—197°, undepressed by a specimen of hemimellitic acid obtained from 1 : 8-naphthalic acid (Graebe and Leonhardt, *Annalen*, 1896, **290**, 218), and identity was confirmed by preparation of the trimethyl ester, m. p. 101—102° (Found: C, 57·2; H, 5·0. Calc. for $C_{12}H_{12}O_6$: C, 57·2; H, 4·8%) (Ruzicka, Goldberg, Huyser, and Seidel, *Helv. Chim. Acta*, 1931, **14**, 545, give m. p. 101°).

Condensation of Tropolone-αβ-dicarboxylic Anhydride with Amines.—(*a*) The anhydride (XVII; R = O) (0·01 g.) was heated in alcohol (2 c.c.) with *o*-phenylenediamine; the brown crystalline solid which quickly separated, could not be recrystallised and was recovered from solution in dilute mineral acid. (*b*) The anhydride (0·2 g.) was boiled with acetic acid (3 c.c.) and aniline (0·2 g.) for 1 minute, and the *N-phenylimide* (XVII; R = NPh) (0·15 g.), deposited on cooling, was washed with dilute acid and crystallised from acetic acid; yellow plates, m. p. 243—245° (Found: N, 5·4. $C_{15}H_9O_4N$ requires N, 5·2%), were obtained. Addition of sodium hydroxide to an alcoholic solution produced an orange colour, and the compound gave a red-brown ferric test. (*c*) The anhydride (0·08 g.), heated with aniline (0·5 g.) for 5 minutes on the water-bath, gave on dilution with ether the *compound* (XVIII), which crystallised from a large volume of acetic acid in scarlet plates (0·12 g.), m. p. 281—283° (Found: N, 8·0. $C_{21}H_{14}O_3N_2$ requires N, 8·2%). It was insoluble in dilute acids, gave a brown ferric test, and yielded the anhydride (XVII; R = O) when boiled with sodium hydroxide solution. The compound (XVIII) was also formed similarly from the *N*-phenylimide and aniline.

Our thanks are offered to the Commonwealth Scientific Research Organisation for Overseas Studenships (to W. D. C.), to the University of Western Australia for a Hackett Research Studentship (to P. R. J.), and to Imperial Chemical Industries Limited for a grant which has defrayed some of the expenses of the research.

The University, Sheffield, 10. [*Received, May 30th*, 1952.]

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711. *New Syntheses of Heterocyclic Compounds. Part XVIII.** 2 : 10-*Diazaphenanthrenes by Application of the Stieglitz Rearrangement.*

By S. S. Berg and V. Petrow.

9-Amino-1 : 3-dimethyl-9-phenyl-2-azafluorene (II; R = NH_2) has been transformed into 9-amino-1 : 3-dimethyl-2 : 10-diazaphenanthrene (V), (i) by conversion into the chloroamine (III), followed by Stieglitz rearrangement to 1 : 3-dimethyl-9-phenyl-2 : 10-diazophenanthrene (VI) and aminolysis to (V), and (ii) directly by reaction with potassium nitrate–potassamide in liquid ammonia.

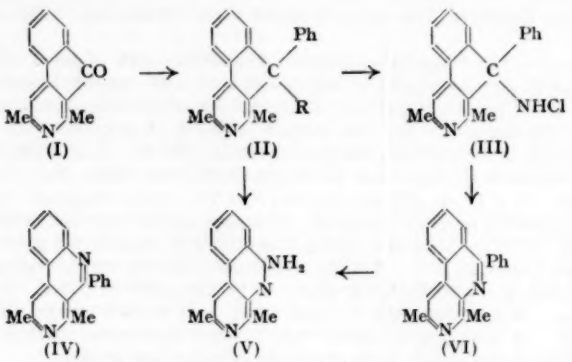
Whereas the dose of picrotoxin required to counteract increasing degrees of barbiturate anæsthesia follows a logarithmic pattern, a linear relation holds in the case of the analeptic drug 9-amino-1 : 3-dimethyl-2 : 10-diazaphenanthrene (V). The advantage thereby conferred upon the latter is nevertheless outweighed by certain difficulties inherent in its preparation by the method outlined in Part V (Petrow, *J.*, 1946, 200). In particular the

* Part XVII, *J.*, 1952, 3358.

use of hydrazoic acid in the conversion of 1 : 3-dimethyl-2-azafluorenone (I) into 9-hydroxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene involves an element of danger which cannot be fully eliminated by close attention to experimental detail. We have, therefore, considered alternative routes to (V) and now report a process which is apparently free from hazard.

Our first experiments were directed to a study of novel procedures for effecting the Beckmann rearrangement of 1 : 3-dimethyl-2-azafluorenone oxime, but unfortunately none of these proved successful (cf. Part V, *loc. cit.*). We then turned our attention to the Stieglitz rearrangement (see Porter, " Molecular Rearrangements," Chemical Catalog. Co. Inc., N.Y., 1928, pp. 30—33) whereby we hoped to convert (I) directly into compounds of the desired character.

Pinck and Hilbert (*J. Amer. Chem. Soc.*, 1937, **59**, 8) have previously shown that 9-chloroamino-9-phenyl-9-fluorene is readily converted into 9-phenylphenanthridine by dry sodium methoxide in anhydrous pyridine. When potassium amide–nitrate in liquid ammonia is used to effect the rearrangement, 9-aminophenanthridine is formed in >60% yield, presumably by way of the 9-phenyl-derivative which then undergoes aminolysis (White and Bergstrom, *J. Org. Chem.*, 1942, **7**, 497; see also below). A further extension of these two reactions is now recorded.



Treatment of 1 : 3-dimethyl-2-azafluorenone (I) with phenylmagnesium bromide led to the formation of 1 : 3-dimethyl-9-phenyl-2-azafluoren-9-ol (II; R = OH) in 70% yield. Reaction of this product with phosphorus pentachloride in anhydrous toluene led to the smooth production of 9-chloro-1 : 3-dimethyl-9-phenyl-2-azafluorene (II; R = Cl) The compound thus obtained proved noticeably more stable than its carbocyclic analogue (Pinck and Hilbert, *loc. cit.*). Its conversion into 9-amino-1 : 3-dimethyl-9-phenyl-2-azafluorene (II; R = NH_2) was ultimately achieved, however, though in only 20% yield, by treatment with potassamide in liquid ammonia.

Reaction of (II; R = NH_2) with hypochlorous acid led to formation of the *N*-chloroamine (III). The latter, on treatment with anhydrous sodium methoxide in dry pyridine passed into 1 : 3-dimethyl-9-phenyl-2 : 10-diazaphenanthrene (VI) (Petrow, *loc. cit.*) in only 20% yield, rearrangement being accompanied by much tar formation. The corresponding 7 : 10-diazaphenanthrene (IV) was not obtained.

Conversion of (VI) into the analeptic drug 9-amino-1 : 3-dimethyl-2 : 10-diazaphenanthrene (V) was effected in moderate yield by treatment with potassamide in liquid ammonia. Application of the White and Bergstrom procedure (*loc. cit.*) to (II), proved less satisfactory, as the product formed in this case was admixed with much resinous material, isolation of (V) being ultimately effected *via* the picrate.

Experimental

M. p.s are uncorrected. Microanalyses are by S. Bance, B.Sc., A.R.I.C., May and Baker, Ltd.

Aminolysis of 9-Phenylphenanthridine.—9-Phenylphenanthridine (2·2 g.; Morgan and Walls, *J.*, 1931, 2447) and potassamide (from 0·5 g. of potassium) in liquid ammonia (10 ml.) was kept at

room temperature in a sealed tube for 48 hours. The ammonia was allowed to evaporate at room temperature and the residue treated with benzene and then carefully with water. The benzene layer was separated and dried, and the solvent removed. The residue, on crystallisation from ethanol, yielded 9-aminophenanthridine (600 mg.), m. p. 188—190° (Found: C, 80·1; H, 5·1; N, 14·7. Calc. for $C_{13}H_{10}N_2$: C, 80·4; H, 5·2; N, 14·5%) not depressed in admixture with an authentic specimen (Morgan and Walls, *J.*, 1932, 2225).

1 : 3-*Dimethyl*-9-*phenyl*-2-*azafluoren*-9-*ol* (II; R = OH).—A Grignard solution prepared from magnesium (10 g.), bromobenzene (87 g.), and anhydrous ether (150 ml.) was treated with 1 : 3-dimethyl-2-azafluorenone (58 g.) during 30 minutes, with ice-cooling and vigorous stirring. An exothermic reaction occurred accompanied, after a few minutes, by separation of crystalline material. The mixture was heated under reflux for 1 hour and then cooled with ice, anhydrous ether (100 ml.) was added, and the magnesium complex was collected, washed with dry ether, and decomposed by 10 minutes' refluxing with 2N-sulphuric acid (5 l.). After ice-cooling, the crystalline sulphate was collected and decomposed with 25% sodium hydroxide solution at 5—10°, and the base extracted with ether (3 × 1200 ml.) and purified from light petroleum (3 l.; b. p. 80—100°). 1 : 3-*Dimethyl*-9-*phenyl*-2-*azafluoren*-9-*ol* (52%) formed prisms, m. p. 183—184° (Found: C, 83·2; H, 5·8; N, 4·8. $C_{20}H_{17}ON$ requires C, 83·6; H, 5·9; N, 4·9%).

9-*Chloro*-1 : 3-*dimethyl*-9-*phenyl*-2-*azafluorene* (II; R = Cl).—1 : 3-Dimethyl-9-phenyl-2-azafluoren-9-ol (15 g.), phosphorus pentachloride (15 g.), and anhydrous toluene (100 ml.) were cautiously mixed. Reaction occurred with separation into two layers, after which the mixture was heated under reflux for 30 minutes. After ice-cooling, the separated solids were collected and treated with 2N-sodium hydroxide at 5—10°, and the base crystallised from light petroleum (50 ml.; b. p. 60—80°). 9-*Chloro*-1 : 3-*dimethyl*-9-*phenyl*-2-*azafluorene* (14 g.) formed prisms, m. p. 114—116° (Found: N, 4·7; Cl, 11·6. $C_{20}H_{16}NCl$ requires N, 4·6; Cl, 11·6%).

9-*Amino*-1 : 3-*dimethyl*-9-*phenyl*-2-*azafluorene* (II; R = NH_2).—The foregoing compound (10 g.) and potassamide (from 1·3 g. of potassium) in liquid ammonia (25 ml.) were kept for 3 days at room temperature in a sealed tube. After the ammonia had been allowed to evaporate, the residue was treated with benzene and ice-water, the benzene layer removed, filtered from tar, and dried over potassium hydroxide, and the solvent removed. The sticky residue was crystallised five times from benzene–ligroin (b. p. 80—100°), to give 9-*amino*-1 : 3-*dimethyl*-9-*phenyl*-2-*azafluorene* (2·1 g.) as faintly brown crystals, m. p. 116—120° (Found: C, 84·4; H, 6·6; N, 9·7. $C_{20}H_{18}N_2$ requires C, 83·9; H, 6·3; N, 9·8%). The *picrolonate* separated from methanol in yellow prismatic needles, m. p. >280° (Found: C, 43·8; H, 3·3; N, 10·6. $C_{20}H_{18}N_2,2C_{10}H_8O_5N_4$ requires C, 44·2; H, 3·2; N, 10·3%), and could be conveniently used for purification of the base, its decomposition being effected by lithium hydroxide.

9-*Chloroamino*-1 : 3-*dimethyl*-9-*phenyl*-2-*azafluorene* (III).—The foregoing compound (2·9 g.) in ethanol (75 ml.) containing dry hydrogen chloride (700 mg.) was treated at 0—5°, with mechanical stirring, with freshly prepared N-potassium hypochlorite (20 ml.). After 1 hour the mixture was diluted with ice-water (30 ml.), and the precipitated solids were collected and crystallised twice from benzene. 9-*Chloroamino*-1 : 3-*dimethyl*-9-*phenyl*-2-*azafluorene* formed pale yellow prisms, m. p. 125—128° (Found: N, 8·5; Cl, 10·8. $C_{20}H_{17}N_2Cl$ requires N, 8·7; Cl, 11·1%).

1 : 3-*Dimethyl*-9-*phenyl*-2 : 10-*diazaphenanthrene* (VI).—9-Chloroamino-1 : 3-dimethyl-9-phenyl-2 : 10-diazaphenanthrene (2·0 g.) in anhydrous pyridine (20 ml.) was treated with anhydrous sodium methoxide (2·0 g.) with mechanical stirring. After being kept overnight the dark red solution was taken to dryness under reduced pressure and the product extracted with benzene. Purification *via* the picrate, m. p. 204—207°, followed by crystallisation from aqueous methanol, afforded 1 : 3-dimethyl-9-phenyl-2 : 10-diazaphenanthrene (400 mg.), silky needles, m. p. 129—131° (Found: C, 84·1; H, 5·6; N, 10·1. Calc. for $C_{20}H_{16}N_2$: C, 84·5; H, 5·6; N, 9·9%) not depressed in admixture with an authentic specimen (Petrow, *loc. cit.*).

9-*Amino*-1 : 3-*dimethyl*-2 : 10-*diazaphenanthrene* (V).—(*a*) The foregoing compound (2·3 g.) and potassamide (from 0·5 g. of potassium) in liquid ammonia (10 ml.) was kept at room temperature in a sealed tube for 48 hours. The product, after crystallisation from ligroin, furnished 9-amino-1 : 3-dimethyl-2 : 10-diazaphenanthrene (450 mg.), pale brown cubes, m. p. 187—189° (Found: C, 75·1; H, 5·7; N, 18·9. Calc. for $C_{14}H_{13}N_3$: C, 75·3; H, 5·8; N, 18·8%) not depressed in admixture with an authentic specimen. The picrate, m. p. 260—262°, likewise did not depress the m. p. of an authentic specimen (Petrow, *loc. cit.*).

(*b*) 9-Amino-1 : 3-dimethyl-9-phenyl-2-azafluorene (3·0 g.), potassium nitrate (1·6 g.), and potassamide (from 2·0 g. of potassium) in liquid ammonia (20 ml.) containing ferric nitrate (50 mg.) was set aside at room temperature in a sealed tube for 5 days. The product, admixed with

much resinous material, was shaken with benzene, and the resulting solution, after filtration, etc., treated with picric acid. The resulting picrate (300 mg.), after purification from ethanol, formed yllow needles, m. p. 259—262°, not depressed in admixture with an authentic specimen. The regenerated base, pale brown cubes, m. p. 187—189° (Found: C, 75·1; H, 5·6: N, 19·0. Calc. for $C_{14}H_{12}N_2$: C, 75·3; H, 5·8; N, 18·8%) after crystallisation from ligroin, likewise did not depress the m. p. of an anthentic specimen.

One of us (S. S. B.) thanks the Directors of May and Baker Ltd. for research facilities.

MAY & BAKER, LTD., DAGENHAM.
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712. *Pyrimidines. Part II.* The Ultra-violet Absorption Spectra of Some Monosubstituted Pyrimidines.*

By (MISS) M. P. V. BOARLAND and J. F. W. MCOMIE.

The ultra-violet absorption spectra of a number of monosubstituted pyrimidines in aqueous buffer solutions and/or in ethanol have been measured. All the compounds examined showed bathochromic shifts which are tabulated, together with the corresponding shifts in the molecular extinction coefficients.

ALTHOUGH the ultra-violet absorption spectra of polysubstituted pyrimidines and purines have been fairly extensively examined, very little work has been reported on the monosubstituted compounds. Indeed, apart from the spectrum of pyrimidine itself, the spectra of only six simple monosubstituted pyrimidines have been investigated, namely, 2-hydroxy- (Brown, *Nature*, 1950, **165**, 1010), 4-hydroxy- (Albert, Brown, and Cheeseman, *J.*, 1951, 474), 2-amino- (Stimson, *J. Amer. Chem. Soc.*, 1949, **71**, 1470), 4-amino- (Williams, Ruehle, and Finkelstein, *ibid.*, 1937, **59**, 526; Cavalieri and Bendich, *ibid.*, 1950, **72**, 2587), 5-amino- (Whittaker, *J.*, 1951, 1565), and 4-methyl-pyrimidine (Marshall and Walker, *J.*, 1951, 1004). Since it seemed probable that a study of the spectra of the monosubstituted pyrimidines would throw light on the spectra of the more complex pyrimidine derivatives, the present work was undertaken and subsequently extended to include some polysubstituted pyrimidines (Part III, succeeding paper).

TABLE 1.

Compound	pKa_1	pKa_2	pH of aq. soln.	Water $\lambda_{max.}$ (mμ)	Water $\log_{10}\varepsilon_{max.}$	Ethanol $\lambda_{max.}$ (mμ)	Ethanol $\log_{10}\varepsilon_{max.}$
Pyrimidine	1·31 [1]	—	0·0	242	3·60 [1]	—	—
			H_2O	243	3·38	239	3·36
				272	2·46	244	3·38
						278—280	2·52
2-Methylpyrimidine	—	—	0·0	251—252	3·87	—	—
			6·98	*248*	3·46	*249*	3·45
4-Methylpyrimidine	2·0 [2]	—	0·0	244	3·70 [2]		
			7·0	*244*	3·53	*245*	3·41
2-Phenylpyrimidine	—	—	0·0	256—258	4·06	—	—
				287	3·92		
			6·98	*251*	4·18	*257*	4·28
2-Chloropyrimidine	<1·0	—	0·0	209	3·76	—	—
				251	3·43		
			6·98	209	3·75	*252*	3·19
				251	3·43	282—283	2·23
4-Chloropyrimidine hydrochloride	—	—	—	—	—	*248*	3·51
5-Chloropyrimidine	—	—	0·0	211—212	3·74	—	—
				260	3·41		
			6·98	211	3·85	*258*	3·34
				258	3·38	293	2·52

* *J.*, 1951, 1218, is considered to be Part I in this series.

TABLE 1—*continued.*

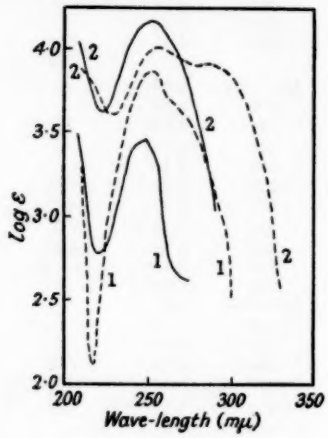
Compound	pKa_1	pKa_2	pH of aq. soln.	Water $\lambda_{max.}$ (mμ)	Water $\log_{10} \varepsilon_{max.}$	Ethanol $\lambda_{max.}$ (mμ)	Ethanol $\log_{10} \varepsilon_{max.}$
5-Bromopyrimidine	—	—	0·0	219·5	3·94	—	—
				265	3·58		
			6·98	216·5	4·02	217·5	3·87
				261	3·46	*261*	3·33
						294	2·53
2-Methylthiopyrimidine	—	—	0·0	214·5	3·39	—	—
				255	4·16		
				310	3·54		
			6·98	*250*	4·12	*251*	4·20
						286	3·30
2-Methoxypyrimidine	—	—	0·0	273—274	3·69	—	—
				309	2·85		
			6·98	*264*	3·68	*267·5*	3·65
2-Aminopyrimidine	3·54 [3]	—	3·0	220	4·10 [4]	—	—
				300	3·58		
			7·0	225	4·04	227	4·22
				292	3·51	*297*	3·59
4-Aminopyrimidine	5·71 [3]	—	0·0	246	4·27 [5]	—	—
			7·73	234	4·08 [6]	236	4·30
				268	3·55	*272—273*	3·71
			13	233	4·26 [5]	—	—
				268—269	3·72		
5-Aminopyrimidine	2·60 [7]	—	1·0	253	4·16 [7]	—	—
				332	3·57		
			H_2O	236	4·04	246	4·10
				298	3·49	*315*	3·50
2-Hydroxypyrimidine	2·24	9·17 [8]	0·3	309	3·75 [8,9]	—	—
			6·1	215	4·0		
				299	3·66		
			13	*290*	3·66		
4-Hydroxypyrimidine	1·85	8·59 [9]	0·0	225	4·18	—	—
				252—254	3·65		
			4·88	227·5	3·97		
				258 inf.	3·74		
			13	227	4·04		
				264—265	3·56		
2-Mercaptopyrimidine	~1·3	7·2	0·0	208	3·87	—	—
				285	4·51		
				378	3·18		
			4·9	278	4·33		
				346	3·42		
			13	231	3·69		
				270	4·23		
4-Mercaptopyrimidine	<1	6·7	0·0	306	4·30	—	—
			4·5	285	4·03		
				327	3·91		
			13	*292—294*	4·04		
Pyrimidine-4-carboxylic acid	—	—	0·0	257	3·57	—	—
			13	*253*	3·51		
Pyrimidine-5-carboxylic acid	—	—	13	*245—246*	3·31	—	—

[1] Jones and Whittaker, forthcoming publication. [2] Marshall and Walker, *J.*, 1951, 1004. [3] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [4] Stimson, *J. Amer. Chem. Soc.*, 1949, **71**, 1470. A redetermination in 1952 gave 3·51 as $\log_{10} \varepsilon$ for the 292-mμ band for the neutral molecule (private communication). [5] Williams, Ruehle, and Finkelstein (*ibid.*, 1937, **59**, 526) report for 4-aminopyrimidine in acid and alkaline solution the values 246, 4·05, and 232, 4·00; 274, 3·56 respectively. [6] Cavalieri and Bendich (*ibid.*, 1950, **72**, 2587) give the values 232, 4·05; 265, 3·58, for the neutral molecule. [7] Whittaker, *J.*, 1951, 1565. [8] Brown, *Nature*, 1950, **165**, 1010. [9] Albert, Brown, and Cheeseman (*J.*, 1951, 474) give the following values for 4-hydroxypyrimidine at pH 0·3, 6·3, and 13; cation, 225, 4·00; neutral molecule, 225, 3·83; anion, 229, 4·07, and 265, 3·68.

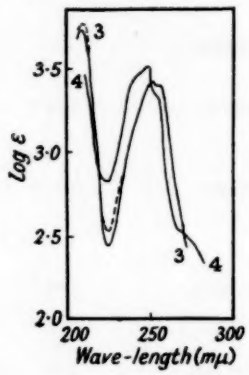
As Marshall and Walker (*loc. cit.*) have observed, much of the earlier work on pyrimidine derivatives containing one or more potentially tautomeric groups (OH, SH, or NH_2) is of doubtful value since the measurements were made without reference to pK_a values and often without control of pH. Consequently, the results obtained referred to a mixture

of ions and neutral molecules, whose composition was unknown. In the present work, following the procedure of Marshall and Walker, the pK_a value of the pyrimidine to be examined determined the pH of the buffer solution to be used as the solvent. The pK_a values, the wave-lengths of maximum extinction, and the logarithms of the molecular extinction coefficients are recorded in Table 1 and the Figures. In addition, the light absorptions of the non-tautomeric pyrimidines were measured in ethanol, since the maxima

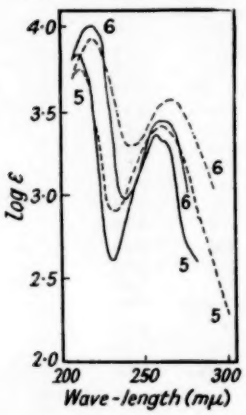
FIGS. 1—2. (1) 2-*Methyl-*; (2) 2-*phenyl-pyrimidine.*



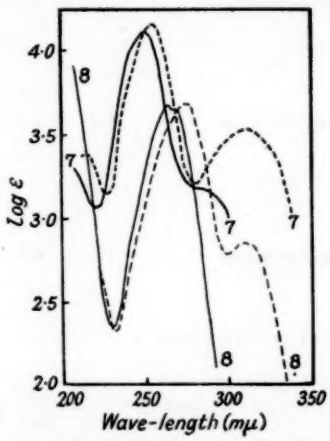
FIGS. 3—4. (3) 2-*Chloro-pyrimidine*; (4) 4-*chloro-pyrimidine hydrochloride.*



FIGS. 5—6. (5) 5-*Chloro-*; (6) 5-*bromo-pyrimidine.*



FIGS. 7—8. (7) 2-*Methylthio-*; (8) 2-*methoxypyrimidine.*



In these and all other Figures, — — — refers to acid, ——— to neutral, and · · · · to alkaline solution.

for many compounds are usually displaced in this medium which was frequently used by earlier workers.

The curves are in general very similar to those reported by Marshall and Walker, confirming their view that the extra methyl group in their compounds would have very little effect on the characteristic spectrum of a pyrimidine containing a potentially tautomeric group. From a comparison of these graphs with those of Marshall and Walker, the same conclusions as those reached by them may be drawn concerning the structure of potentially tautomeric monosubstituted pyrimidines in neutral solution. For example, the light-

extinction curve of 2-methylthiopyrimidine (Fig. 7) in neutral solution is very similar to that of 2-mercaptopyrimidine (Fig. 9) in alkaline solution. It is quite different from the light-extinction curve of the neutral 2-mercaptopyrimidine molecule (Fig. 9) which is closely similar to that of 1 : 4 : 6-trimethyl-2-pyrimidthione. It seems probable therefore that 2-mercaptopyrimidine in neutral solution exists mainly in the thione structure. From similar arguments, it is likely that 2- and 4-hydroxy- and 4-mercapto-pyrimidine also exist in the 2- and 4-pyrimidone and the 4-pyrimidthione form respectively. The anions

FIG. 9. *2-Mercaptopyrimidine.*

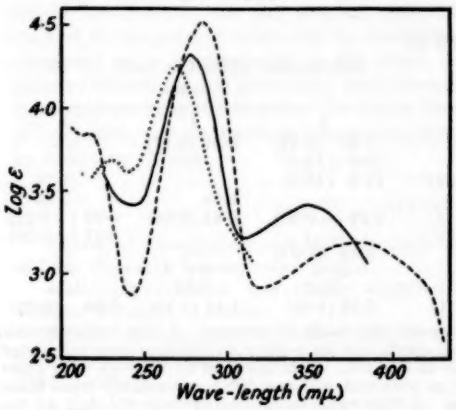
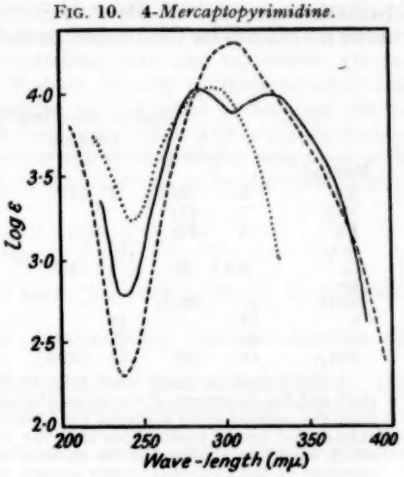
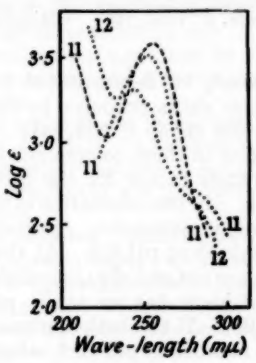


FIG. 10. *4-Mercaptopyrimidine.*





FIGS. 11—12. (11) *Pyrimidine-4-*; (12) *pyrimidine-5-carboxylic acid.*

will, of course, have the same structures whether they are derived from hydroxy- (mercapto-)pyrimidines or from pyrimidones (pyrimidthiones).

The ultra-violet absorption spectrum of pyrimidine in aqueous solution consists of at least three bands, one below 200 (probably of high intensity, by analogy with benzene), one at 243 (log $\varepsilon = 3{\cdot}38$), and a broad band between 260 and 290 mμ with a maximum at 272 mμ (log $\varepsilon = 2{\cdot}46$) (Jones and Whittaker, forthcoming publication; see also Halverson and Hirt, *J. Chem. Phys.*, 1951, **19**, 711, which contains earlier references). It will be seen from Table 1 and the Figures that nuclear substitution causes a bathochromic shift of the absorption bands and that, with the possible exception of 2-mercaptopyrimidine, the bands of longer wave-length have lower intensities than those of shorter wave-length for a given compound. It thus seems reasonable to suppose that the bands whose maxima are italicised in Table 1 are due to the displacement of the 243- or 244-mμ band of pyrimidine

in water and alcohol respectively. In the same way, the bands of shortest and longest wave-length are probably related to the bands <200 and >270 mμ of pyrimidine. Doub and Vandenbelt (*J. Amer. Chem. Soc.*, **1947**, **69**, 2714; **1949**, **71**, 2414) have similarly correlated the ultra-violet absorption spectra of mono- and poly-substituted benzenes with benzene itself. The bathochromic shifts for a single substituent in different positions in the pyrimidine nucleus are given in Table 2. It may be seen that for a single substituent, the bathochromic shift varies according to the position of the substituent in the pyrimidine ring. Thus, the 2-substituents form a series which may be written in the order of increasing bathochromic shift: $Me < MeS < Ph < Cl < MeO < S^- \ll O^- < NH_2$. A similar series is obtained for the 4-substituents: $Me < Cl < CO_2^- < O^- < NH_2 \ll S^-$. Andrisano

TABLE 2.[1]

	Shift in wave-length						Shift in mol. extinction coeff. (× 10^{-3})					
	Position						Position					
Radical	2		4		5		2		4		5	
Me	5	(5)	1	(1)	—		0·48	(0·42)	0·99	(0·17)	—	
MeS	7	(7)	—		—		10·8	(13·4)	—		—	
Ph	8	(13)	—		(12)[5]		12·6	(16·6)	—		(9·7)	
CO_2^-	—		10		2·5		—		0·84		−0·36	
Cl	9·5[3]	(8)	5[3]	(4)[3]	15	(14)	0·29	(−0·85)	0·84	(0·84)	0·03	(−0·22)
Br	—		—		18	(17)	—		—		0·47	(−0·26)
MeO	21	(23·5)	—		—		2·39	(2·07)	—		—	
S^-	27		48		—		14·6		8·6		—	
O^-	47		21·5		—		2·17		1·23		—	
NH_2[4]	49	(53)	25	(28·5)	55	(71)	0·86	(1·49)	1·13	(2·73)	0·69	(0·73)

[1] The values in parentheses refer to the measurements made in ethanol. [3] The bathochromic shift and the increment of the molecular extinction coefficient for 4-chloropyrimidine were calculated from the measurement made on the hydrochloride in ethanol. It is assumed by analogy with other chloro- and bromo-pyrimidines that the value thus obtained will not differ appreciably from those which would be observed in an aqueous medium. [3] This value is calculated from the $\lambda_{max.}$ of the envelope of the extinction curve instead of the observed $\lambda_{max.}$ (cf. Fig. 3). [4] The infra-red spectra of 2- and 4-aminopyrimidines indicate that these compounds probably exist in the NH_2 form rather than the tautomeric = NH form (Short and Thompson, *J.*, 1952, 168). [5] Maggiolo and Russell, *J.*, 1951, 3297.

and Modena (*Gazzetta*, **1951**, **81**, 405), from a study of 2-substituted 4 : 6-dimethylpyrimidines, have reported the following bathochromic shifts produced by the 2-substituent: MeS (4) < Me,Ph (5) < Cl (8·5) < MeO (18) < SH (32·5) < NH_2 (41) < OH (48). The order of the series for substituents in the 2-position in these compounds is very similar to that obtained from the monosubstituted compounds except for the first three members where the differences are only of the order of 1 mμ. In the calculation of the bathochromic shifts for 2-hydroxy- and 2-mercapto-4 : 6-dimethylpyrimidine, Andrisano and Modena use the wave-length of maximum extinction obtained at pH 5·6. At this pH both these compounds will exist as neutral molecules which are not strictly comparable with the non-tautomeric pyrimidines (4 : 6-dimethyl-2-pyrimidthione has an acidic pK_a value of 8·5 and 4 : 6-dimethyl-2-pyrimidone will be less acidic). If the bathochromic shifts for these substituents are calculated from the wave-length maxima at pH 12·9, when the compounds should exist entirely as anions, the values 23 mμ for S^- and 43 mμ for O^- are obtained which are in better agreement with the values obtained from the monosubstituted pyrimidines. It is seen that the bathochromic shifts obtained from a study of the dimethylpyrimidines are less than those obtained from the monosubstituted derivatives. This is in agreement with our observations on polysubstituted pyrimidines, where it has frequently been found that methyl groups in the 4- and the 6-position prevent other substituents from exerting their full bathochromic effect.

Following Stimson's suggestion (*J. Amer. Chem. Soc.*, **1949**, **71**, 1470), Andrisano and Modena (*loc. cit.*) classified the 4 : 6-dimethylpyrimidines which they examined as symmetrical, quasi-symmetrical, or asymmetrical. A pyrimidine which is symmetrically disposed about a plane perpendicular to the plane of the ring and passing through carbon atoms 2 and 5 is termed symmetrical. According to Andrisano and Modena, the wave-length of maximum extinction in a symmetrical pyrimidine remains constant throughout

the pH range, although the extinction coefficient varies. They termed compounds which are formally symmetrical and whose wave-length maxima varied with pH to a certain extent, quasi-symmetrical. Substituents falling into the latter class were Me, Ph, and SMe. The 2-substituted 4 : 6-dimethylpyrimidines whose maximum wave-length varied continuously with pH were termed asymmetrical by Andrisano and Modena who placed substituents such as OH, OMe, SH, and NH_2 in this class. Stimson (*loc. cit.*), on the other hand, classified pyrimidines such as barbituric acid and 5-ethyl-4 : 6-dihydroxy-2-mercapto-pyrimidine as symmetrical pyrimidines. She did not however record measurements made above pH 11 which is probably below at least one of the acidic dissociation constants of this type of compound. It is likely therefore that at higher pH values the maximum would be shifted. In the simpler compounds containing only one tautomeric group, studied in the present work and by Andrisano and Modena, the only pyrimidines which are observed to be symmetrical in the strict sense defined by the latter authors are the 2-chloro-compounds. These have exceptionally low basic pK_a values and probably do not form cations in acid solution. It seems therefore that the shifting of the maximum with pH depends, not so much on the actual symmetry of the molecule, as on the formation of an anion or cation.

Experimental

Source of Pyrimidines.—2-Methylpyrimidine was kindly supplied by Dr. E. C. Kornfeld, of Lilly Research Laboratories, U.S.A.

4-Methylpyrimidine was kindly supplied by Dr. James Walker, National Institute for Medical Research, London.

2-Chloropyrimidine, 4-chloropyrimidine hydrochloride, 2- and 4-mercaptopyrimidine, and pyrimidine-5-carboxylic acid were prepared by known methods (Boarland and McOmie, *J.*, 1951, 1218).

5-Chloropyrimidine, 2-phenylpyrimidine, and pyrimidine oxalate were generously supplied by Dr. B. Lythgoe of Cambridge.

2-Aminopyrimidine. The commercial product of Eastman Kodak Company was recrystallised from benzene before use.

4-Aminopyrimidine was a gift from Dr. D. J. Brown, Australian National University, London.

4-Hydroxypyrimidine was prepared from 2-thiouracil by Brown's method (*J. Soc. Chem. Ind.*, 1950, **69**, 353).

A solution of pyrimidine in alcohol was obtained by dissolving pyrimidine oxalate (4·0 mg.) in ethanol (9·95 c.c.) and N-sodium hydroxide (0·05 c.c.). The ethanol in the control cell contained an equivalent quantity of sodium oxalate.

For 5-bromopyrimidine and pyrimidine-4-carboxylic acid see McOmie and White, forthcoming publication.

2-Methylthiopyrimidine. 2-Mercaptopyrimidine (2·2 g.) and methyl sulphate (2·0 c.c.) were shaken in aqueous sodium hydrogen carbonate (1·65 g. in 40 c.c.) at room temperature for 2 hours. The pyrimidine slowly dissolved, the colour fading to pale yellow. Extraction with ether (150 c.c.) gave a bright yellow oil. Three distillations under reduced pressure gave 2-methylthiopyrimidine as a colourless liquid, b. p. 109°/28 mm. (1·54 g., 62%), n_D^{14} 1·5880. Johnson and Joyce (*J. Amer. Chem. Soc.*, 1916, **38**, 1385) report b. p. 99—100°/14 mm., n_D^{20} 1·5856, for the compound prepared by zinc dust reduction of 4-chloro-2-methylthiopyrimidine.

2-Methoxypyrimidine. 2-Chloropyrimidine (5·0 g.) in methanol (20 c.c.) was added to a solution of sodium methoxide [from sodium (1·0 g.)] in methanol (30 c.c.). An exothermic reaction took place with immediate separation of sodium chloride. After several hours at room temperature, the solution was filtered and the methanol removed by distillation. The residue was distilled under reduced pressure from a quantity of sodium chloride which had separated from the methanolic solution. 2-Methoxypyrimidine was obtained as a colourless liquid (3·0 g., 63%), b. p. 72·5°/22 mm., n_D^{14} 1·5023, in good agreement with Albert and Brown's observations (personal communication).

Physical Measurements.—Absorption spectra. These were measured with a Unicam S.P. 500 quartz spectrophotometer at the pH values recorded in the Table. The buffer solutions were : 0·2N-acetate (for pH 4·0—5·0), M/15-phosphate (pH 6·98), together with N- (pH 0) and 0·1N-hydrochloric acid (pH 1·0), and 0·1N-sodium hydroxide (pH 13). Values of wave-lengths below 235 mμ are probably only correct to within ±2 mμ owing to the initial incorrect adjustment of the instrument.

Potentiometric titrations. The pH of the solution was measured during titration with a Doran pH Indicator standardised against 0·05M-potassium hydrogen phthalate buffer solutions, a Doran Linear (0—13 pH) Alkacid glass electrode being used. The pK_a values were calculated from the pH readings and are probably correct within ±0·2 pH unit.

The authors thank Professor A. Albert and Mr. G. E. Coates for their helpful advice on potentiometric titrations, Mr. M. Marshall for the measurement of some of the ultra-violet spectra, and the Department of Scientific and Industrial Research for the award of a Maintenance Grant to one of them (M. P. V. B.)

THE UNIVERSITY, BRISTOL. [*Received, May 5th,* 1952.]

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713. *Pyrimidines. Part III.* The Ultra-violet Absorption Spectra of Some Polysubstituted Pyrimidines.*

By (MISS) M. P. V. BOARLAND and J. F. W. MCOMIE.

Measurements of the ultra-violet absorption spectra of polysubstituted pyrimidines containing not more than one potentially tautomeric group are reported and discussed. The results indicate that the position of the absorption maxima for these compounds can be predicted approximately by adding the bathochromic shifts of the individual substituents to the appropriate wave-length maximum in the spectrum of pyrimidine itself. The same appears to be true for the molecular extinction coefficients. Both relations hold for ethanolic as well as aqueous solutions.

The so-called "dithiourimido-acetylacetone" has been shown to be a simple 1 : 1 molecular complex of thiourea with 2-mercapto-4 : 6-dimethylpyrimidine. Two similar complexes are described.

THE ultra-violet light absorption of pyrimidines containing two or more potentially tautomeric groups has been fairly widely studied. Until recently, however, there has been little work reported on pyrimidines containing a single functional group. In order to gain further information about the structure of potentially tautomeric pyrimidines in aqueous solution, Marshall and Walker (*J.*, 1951, 1004) investigated the absorption spectra of a considerable number of these compounds and a representative list of references to the earlier literature is published in their paper. In Part II * the absorption spectra of monosubstituted pyrimidines were reported. The present paper describes our results with polysubstituted pyrimidines which contain not more than one potentially tautomeric group (*e.g.*, OH, SH, NH_2). The measurements were carried out in buffer solutions following the procedure of Part II; non-tautomeric pyrimidines were also examined in ethanol solution. In general, the light-absorption curves for the types of compounds we have measured resemble those for the related monosubstituted compounds and are not illustrated graphically.

Consideration of the results obtained in Part II in conjunction with published data on polysubstituted pyrimidines indicated that, in compounds containing not more than one potentially tautomeric group, the effect of the individual substituents on both the wave-length of maximum absorption and the extinction coefficient was approximately additive for the middle band of the spectrum (see below). This has been confirmed and extended by a study of all suitable pyrimidines available and the results are set out in Tables 1 and 2. In both Tables, the compounds are arranged in the order of increasing $\lambda_{max.}$. The bands whose maxima are italicised are considered to be the displaced middle band of the pyrimidine spectrum (243 mμ in aqueous solution and 244 mμ in ethanolic solution) (cf. Part II). The column headed $\Delta\lambda$ in the Tables gives the difference between the observed and the calculated wave-length of maximum extinction for the compound under consideration. The calculated wave-length is obtained by adding the sum of the shifts

* Part II, preceding paper.

TABLE 1. *Measurements in aqueous solution.* (*Values for the middle wave-band are in italics.*)

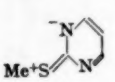
No.	Position of substituent 2	4	6	5	pH	$\lambda_{max.}$ (mμ)	Δλ	$10^{-3}\varepsilon$ (obs.)	$10^{-3}\varepsilon$ (calc.)
1	—	Me	Me	—	0·0	208·5, 247	—	1·9, 4·4	—
					6·98	*246* [1]	10	*4·3*	4·4
2	MeS	Me	—	—	7·0	210, *250* [2]	−10	4·0, *13·8*	14·2
3	MeS	Me	Me	—	5·6	*250* [3]	−20	*12·9*	15·2
4	Me	Me	Me	—	10·2	*251*, 292 [3]	10	*4·2*, 1·4	4·9
5	Ph	Me	Me	—	5·6	*251* [3]	−20	*16·6*	17·0
6	Ph	Me	—	—	—	*252* [6]	0	*22·9*	16·0
7	—	Cl	Cl	—	6·98	*254*	10	*4·6*	4·1
8	Cl	Me	Me	—	5·6	*254·5* [3]	0	*4·7*	4·7
9	Me	Cl	Cl	—	6·98	*257·5*	−5	*6·6*	4·6
10	Cl	Cl	—	—	H_2O	*258* [4]	5	*4·7*	3·5
11	Cl	Cl	Me	—	H_2O	*258* [4]	−5	*5·4*	4·5
12	MeS	—	—	Br	H_2O	218·5, *260·5*	−75	3·3, *21·9*	13·7
13	—	O^-	Me	—	13	230, *261* [5]	−45	10·7, *3·8*	4·6
14	Cl	Cl	Cl	—	—	*263* [10]	5	*4·8*	4·4
15	MeO	O^-	Me	—	13	222, *263* [3]	−235	6·8, *7·4*	7·0
16	MeO	Me	—	—	7·0	*264* [2]	−10	*5·4*	5·8
17	MeO	Me	Me	—	10·2	*264* [3]	−20	*6·6*	6·8
18	—	NH_2	Me	—	13	234, *264* [2]	−50	8·9, *2·8*	4·5
19	Me	NH_2	Me	—	—	235, *265* [7]	−90	10·8, *4·4*	5·0
20	Me	—	—	Br	6·98	219, *267*	10	12·3, *3·0*	5·0
21	S^-	Me	—	—	11	*269* [2]	−20	*17·4*	18·0
22	S^-	Me	Me	—	0·0	223·5, 284	—	13·2, 36·3	—
						356	—	2·6	—
					6·98	217·5, 276	—	12·6, 24·0	—
						332	—	4·7	—
					13	*269* [2]	−30	*19·1*	19·0
23	Cl	—	—	Cl	6·98	219, *272*	45	17·0, *3·2*	2·7
24	Me	NH_2	—	—	—	231, *272* [7]	−10	10·0, *4·0*	4·0
25	Cl	NH_2	—	—	7·0	232, *272* [9]	−55	8·5, *5·0*	3·8
26	MeS	O^-	Me	—	13	247, *274*	15	8·5, *6·8*	15·4
27	Ph	O^-	Me	—	13	231, *277*	35	19·9, *7·4*	17·3
28	Cl	Cl	Cl	Cl	—	232, *278* [11]	5	8·2, *5·2*	4·3
29	S^-	—	—	Cl	13	227, *279*	−60	8·7, *23·4*	17·0
30	Ph	O^-	Cl	—	13	233, *280*	25	21·9, *8·7*	17·1
31	MeS	NH_2	CH_3	—	0·0	241	—	28·2	—
					6·98	225, 248	—	21·9, 12·0	—
						280	40	*7·4*	15·3
32	MeS	NH_2	—	—	0·0	241	—	33·1	—
					6·98	224, *285*	100	19·5, *5·8*	14·3
33	MeS	O^-	Me	Br	13	254, *286*	−45	8·7, *7·4*	15·9
34	NH_2	Me	Me	—	5·6	226, *287* [3]	−70	10·7, *4·6*	5·2
35	NH_2	Me		—	13	225, *289* [2]	−40	12·3, *4·0*	4·3
36	O^-	Me	Me	—	12·9	223, *289* [3]	−30	7·2, *5·0*	6·6
37	O^-	Me	—	—	13	220, *290* [2]	−10	11·5, *5·8*	5·6
38	NH_2	Cl	Me	—	0·0	211·5, 302·5	—	18·6, 6·5	—
					6·98	230, *292*	−60	12·9, *5·1*	5·1
39	—	S^-	Me	—	11·0	*292* [2]	0	*15·9*	12·0
40	—	Me	—	NH_2	13	234, *293* [3]	−60	8·1, *3·5*	4·1
41	NH_2	Cl	—	—	7	229, *296* [9]	−10	13·9, *4·2*	4·1
42	NH_2	Cl	Cl	—	—	233, *298·5* [12]	−35	15·4, *5·9*	5·0
43	NH_2	Me	Me	Br	H_2O	235·5, *301*	−110	19·1, *5·4*	5·7
44	NH_2	—	—	Cl	0·0	233, 325	—	19·5, 3·6	—
					H_2O	235, *311*	40	23·4, *3·7*	3·3
45	O^-	—	—	Cl	13	230, *311*	60	18·2, *4·9*	4·6
46	NH_2	—	—	Br	0·0	235, 326	—	21·9, 3·9	—
					6·98	237, *311·5*	15	19·5, *2·9*	3·7
47	O^-	—	—	Br	13	229, *312*	40	18·6, *4·3*	5·0
48	Cl	Cl	—	NH_2	H_2O	250, *316* [13]	35	15·1, *4·1*	4·2

[1] Basic $pK_a = 2·7$. Andrisano and Modena (*Gazzetta*, 1951, **81**, 405) report 246, 5·6; 246, 3·5, at pH 1·03 and 5·6 respectively. [2] Marshall and Walker, *J.*, 1951, 1004. [3] Andrisano and Modena (*loc. cit.*). [4] Heyroth and Loofbourow, *J. Amer. Chem. Soc.*, 1934, **56**, 1728. [5] Williams, Ruehle, and Finkelstein, *ibid.*, 1937, **59**, 526. [6] Measured in 5% ethanol. [7] Williams, Ruehle, and Finkelstein (*loc. cit.*); measured in 0·005M-NaOH. [8] Basic $pK_a = 2·8$, acidic $pK_a = 8·5$. Andrisano and Modena (*loc. cit.*) report 269, 16·6 for the anion. [9] Stimson, *ibid.*, 1949, **71**, 1470. [10] Uber and Winters, *ibid.*, 1941, **63**, 137; measured in 4% methanol. [11] Uber and Winters (*loc. cit.*); measured in 33% methanol and 67% water. [12] Measured in 5% ethanol. [13] Whittaker, *J.*, 1951, 1565.

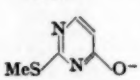
of the individual substituents (given in Table 2, Part II) present in the compound to the wave-length of maximum extinction in the middle band of the pyrimidine spectrum. The extinction coefficients were calculated in the same way and are recorded in the column headed ε(calc.).

It may be seen that, for the majority of compounds, the agreement between the observed and calculated values, both for the wave-length of maximum extinction and for the extinction coefficient, is reasonably good. (This is true for ethanolic as well as aqueous solutions.) There are, however, certain exceptions which merit further discussion. Methyl or chloro-groups in the 4- or 6-position appear to prevent another different substituent in the 2- or 4-position from exerting its full bathochromic effect, with the result that $\Delta\lambda$ has a fairly large negative value. This phenomenon is well shown by compounds **3**, **5**, **13**, **17**, **18**, **19**, **21**, **22**, **34**, **35**, **36**, **38**, and **42** in Table 1 and compounds **34**, **38**, and **42** in Table 2. In these compounds, however, there is fair agreement between the calculated and the observed extinction coefficients.

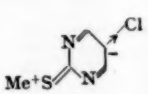
In compounds where the 2-position is occupied by a phenyl or a methylthio-group, and the 4-substituent is an amino- or hydroxy-group, the observed extinction coefficient is very much less than the calculated value (compounds **26**, **27**, **30**, **31**, **32**, and **33**). In these compounds, $\Delta\lambda$ is usually large and positive. Both 2-methylthio- and 2-phenyl-pyrimidine show very high extinction coefficients (10,800 and 12,600 respectively) and presumably therefore there is a high degree of electronic transition as shown in (I) (one canonical form only is shown). Similar conjugation could also occur with 4-aminopyrimidines or anions of 4-hydroxypyrimidines (II) (although probably to a smaller extent, as judged from their lower extinction coefficients—1130 and 1230 respectively). When groups of this type occupy the 2- and the 4-position in one compound (*e.g.*, as in III), they form a " crossed " conjugated system (cf. Braude, *Ann. Reports*, 1945, **42**, 125) which may account for the low observed extinction coefficient. It is interesting that the same effect is not observed when the 2-substituent is methoxyl [*e.g.*, compound **15**], which shows a low individual extinction coefficient (2390). Similar effects have been observed by Russell and Whittaker (forthcoming publication) in 5-phenylpyrimidines where substitution by an amino-group in the 2-position leads to increased conjugation between the rings, but an additional 4-amino-group lessens the intensity of absorption. These authors also found that substitution of an amino-group or similar substituent into the 2- or the 4-position of a 6-phenylpyrimidine apparently completely destroyed the conjugation between the rings.


(I)

(II)


(III)

(IV)


(V)

In compounds of the type (IV; X = Cl or Br), when Y = $-S^-$ or SMe, it is found that the observed value of the extinction coefficient is considerably higher than the calculated value (compounds **12** and **29** in Table 1). When Y = Me, Cl, NH_2, or O^-, the observed and the calculated values of the extinction coefficient are in good agreement (compounds **20**, **23**, **44**, **45**, **46**, and **47** in Table 1). Here again, the individual groups S^- and SMe show high extinction coefficients and hence presumably conjugate fairly extensively with the pyrimidine ring. The presence of a strongly electronegative 5-substituent probably enhances this conjugation, as in (V), leading to the high observed extinction coefficient. The individual groups Me, Cl, NH_2, and O^- show little conjugation with the pyrimidine ring and this is apparently not appreciably increased by the presence of an electronegative 5-substituent. The latter compounds show positive $\Delta\lambda$ values of varying magnitude, whereas when Y = S^- or SMe, the values of $\Delta\lambda$ are fairly large and negative.

Both 5-bromo-4-hydroxy-6-methyl-2-methylthiopyrimidine (**33** in Table 1) and 2-amino-5-bromo-4 : 6-dimethylpyrimidine (**43** in Table 1) have negative values of $\Delta\lambda$ of considerably greater magnitude than those of the corresponding compounds without the bromine in the 5-position (**26** and **34** in Table 1). This may be due to a certain amount of

steric interaction between the neighbouring groups in the 4- and the 6-positions and the 5-bromine atom, which would prevent the bromine from exerting its full bathochromic effect. A similar effect has been observed by Maggiolo and Russell (*J.*, 1951, 3297) with 4- and 6-substituted 5-phenylpyrimidines (compounds 50 and 51, Table 2).

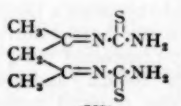
TABLE 2. *Measurements in ethanol.* (*Values for the middle wave-band are in italics.*)

No.	Position of substituent 2	4	6	5	$\lambda_{max.}$ (mμ)	Δλ	$10^{-3}\varepsilon$ (obs.)	$10^{-3}\varepsilon$ (calc.)
1	—	Me	Me	—	*245·5*	−5	*2·0*	2·74
50	—	Cl	—	Ph	*252* [1]	−80	*9·0*	12·9
7	—	Cl	Cl	—	*253*	10	*1·87*	4·08
51	Me	Cl	Cl	Ph	*253* [1]	−160	*6·4*	14·2
8	Cl	Me	Me	—	*254*	0	*3·85*	1·89
9	Me	Cl	Cl	—	*256*	−10	*5·9*	4·5
6	Ph	Me	—	—	*257*	−10	*23·4*	19·17
52	Ph	Me	Me	—	*258* [1]	−10	*20·2*	19·3
12	MeS	—	—	Br	218, *262*	−60	3·85 *37·4*	15·5
20	Me	—	—	Br	218, *266*	0	9·7, *2·1*	2·56
23	Cl	—	—	Cl	219, *268*	20	15·8, *3·1*	1·33
49	Cl	Cl	—	Cl	225, *274*	40	11·7, *4·17*	2·17
31	MeS	NH_2	Me	—	225, *248*		23·4, 11·7	
					282	15	*7·08*	18·7
32	MeS	NH_2	—	—	223·5, *286·5*	70	24·0, *7·24*	18·5
34	NH_2	Me	Me	—	229, *290*	−90	18·6, *7·24*	4·23
38	NH_2	Cl	Me	—	232, *294*	−80	14·4, *4·9*	4·9
42	NH_2	Cl	Cl	—	236, *298·5*	−65	15·5, *4·57*	5·57
43	NH_2	Me	Me	Br	237, *302*	−140	19·5, *4·79*	3·97
47	NH_2	—	—	Br	238, *315·5*	15	19·3, *2·89*	3·63
44	NH_2	—	—	Cl	237, *316*	50	23·2, *3·60*	3·67

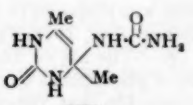
[1] Maggiolo and Russell, *J.*, 1951, 3297.

Although no additive relation has been found for pyrimidines containing more than one potentially tautomeric group, the results obtained so far may prove to be useful in determining the structure of compounds containing not more than one prototropic group. A similar type of additive relation has been reported by Doub and Vandenbelt (*J. Amer. Chem. Soc.*, 1947, **69**, 2714; 1949, **71**, 2414) in disubstituted benzenes where the two substituents are of complementary electronic character (*i.e.*, one *ortho-para*-directing and one *meta*-directing substituent). The relation was found to hold for the secondary, first primary, and second primary bands of the benzene spectrum. Vittum and Brown (*ibid.*, 1947, **69**, 152) studied the effect on the absorption spectrum of substitution in the oxygen-containing ring of the indoaniline dye, phenol-blue. They found that in general the shifts in the wave-length of maximum extinction and the extinction coefficient brought about by two or more substituents agreed closely with the values calculated by adding the shifts for the separate substituent groups.

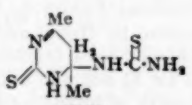
During the preparation of 2-mercapto-4 : 6-dimethylpyrimidine by Evans's method (*J. pr. Chem.*, 1893, **48**, 489) difficulty was found in separating it from the compound formed from two molecules of thiourea and one of acetylacetone. Evans called this compound " dithiourimido-acetylacetone " and suggested it had structure (VI) by analogy with a similar compound formed from urea and acetylacetone which had been described in the previous year by Combes and Combes (*Bull. Soc. chim.*, 1892, **7**, 788). Some years later



(VI)



(VII)



(VIII)

de Haan (*Rec. Trav. chim.*, 1908, **27**, 162) repeated the reaction between urea and acetylacetone and suggested the structure (VII) for " diurimido-acetylacetone." Hale (*J. Amer.*

Chem. Soc., 1915, **37**, 1544) showed that the compound could be formed simply on mixing together concentrated aqueous solutions of thiourea and 2-mercapto-4 : 6-dimethylpyrimidine and put forward (VIII) as the structure of this compound. Since it appeared unlikely that thiourea would add across a double bond in a pyrimidine ring under such mild conditions, we decided to investigate the compound further.

Recently Bray, Lake, and Thorpe (*Biochem. J.*, 1951, **48**, 400) have reported the formation of a 1 : 1 complex between urea and 2-amino-4 : 6-dimethylpyrimidine. We have examined the behaviour of this complex, a similar complex made from thiourea and 2-amino-4 : 6-dimethylpyrimidine, and the "dithiourimido-acetylacetone" in paper-partition chromatography. All three compounds gave two spots whose R_F corresponded exactly to those of the pure components from which the complex was formed. Further, the ultra-violet absorption spectrum of the "dithiourimido-acetylacetone" was the same as that which would be obtained by superimposing the individual spectra of thiourea and 2-mercapto-4 : 6-dimethylpyrimidine. If the "dithiourimido-acetylacetone" had the structure assigned to it by Hale (*loc. cit.*) its ultra-violet spectrum would be expected to be very different from that of a highly conjugated system such as 2-mercapto-4 : 6-dimethylpyrimidine. In the light of these results it is suggested that "dithiourimido-acetylacetone" is simply a 1 : 1 molecular complex of thiourea with 2-mercapto-4 : 6-dimethylpyrimidine. A similar conclusion applies to the other two complexes.

As a continuation of the work on the reaction of thiourea with chloropyrimidines (Part I) two further reactions may be described. Thiourea reacts with 4 : 6-dichloropyrimidine in boiling ethanol, giving *S*-4-mercapto-6-pyrimidylthiuronium chloride. This can be hydrolysed by alkaline solution to 4 : 6-dimercaptopyrimidine in good yield. Under similar conditions, 2 : 5-dichloropyrimidine reacts with thiourea to give the corresponding monothiuronium salt, hydrolysed by sodium hydroxide to 5-chloro-2-mercaptopyrimidine.

Experimental

M. p.s are uncorrected. Microanalyses are by Mr. W. M. Eno, Bristol, and Drs. Weiler and Strauss, Oxford.

Source of Pyrimidines.—Compounds **26** and **31** were kindly supplied by Drs. W. F. Short and D. A. Peak (Boots Pure Drug Co., Ltd., Nottingham). Their purity was checked by m. p. determinations.

Compounds **27**, **30**, **32**, **33**, **38**, and **42** were gifts from Drs. F. L. Rose and R. Hull (Imperial Chemical Industries Limited). The purity of **30** and **33** was checked by chromatography (acetic acid–water–ethyl acetate : 1 : 2 : 3); **27** **32**, **38**, and **42** were purified by vacuum-sublimation.

Compound **6** was kindly sent to us by Drs. J. C. Roberts and T. D. Heyes (Nottingham University); it was purified by vacuum-sublimation.

4 : 6-Dimethylpyrimidine (**I**) was prepared by catalytic reduction of 2-chloro-4 : 6-dimethylpyrimidine by Mr. R. N. Timms (unpublished).

Compounds **12** and **20** were prepared by Mr. I. M. White (forthcoming publication).

Compounds **7** (Hull, *J.*, 1951, 2214), **23** and **45** (English *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1043), **44** (Roblin, Winnek, and English, *ibid.*, 1942, **64**, 567), **46** (English *et al.*, *ibid.*, 1946, **68**, 453), and **47** and **49** (unpublished) were prepared by Mr. E. R. Sayer.

2-Amino-4 : 6-dimethylpyrimidine (**34**) was prepared by the method of Combes and Combes (*Bull. Soc. chim.*, 1892, **7**, 788). It was brominated according to the procedure of Bray, Lake, and Thorpe (*Biochem. J.*, 1951, **48**, 400).

4 : 6-Dihydroxy-2-methylpyrimidine was prepared in 77% yield by using a procedure similar to that described by Huber and Hölscher (*Ber.*, 1938, **71**, 87) for the 2-ethyl derivative.

4 : 6-*Dichloro*-2-*methylpyrimidine* (**9**).—The above dihydroxy-compound (10 g.) was heated under reflux for 2½ hours in a mixture of phosphorus oxychloride (100 c.c.) and dimethylaniline (7 c.c.). Excess of phosphorus oxychloride was removed under reduced pressure and the residue poured on crushed ice. Extraction with ether in the usual way gave the crude product as a pale yellow solid (10·8 g., 84%). Sublimation at 65°/18 mm. gave the pure compound as highly refracting needles, m. p. 49°. Baddiley, Lythgoe, McNeil, and Todd (*J.*, 1943, 383) obtained this compound, m. p. 48—49°, in 75% yield using phosphorus oxychloride alone.

S-4-*Mercapto*-6-*pyrimidylthiuronium Chloride*.—4 : 6-Dichloropyrimidine (2·0 g.) and thiourea (2·0 g.) were heated under reflux in ethanol (80 c.c.) for 1 hour. The colour of the solution rapidly became bright yellow and much solid separated. After removal of the solid and concentration of the filtrate a total yield of 2·9 g. (99%) of crude crystalline material was obtained. Recrystallisation from aqueous ethanol–ether gave pure S-4-*mercapto*-6-*pyrimidylthiuronium chloride* as a pale yellow powder which darkened above 180° and melted at 214° (decomp.) (Found : C, 27·1; H, 3·2; N, 24·9. $C_5H_7N_4S_2Cl$ requires C, 27·0; H, 3·15; N, 25·2%).

4 : 6-*Dimercaptopyrimidine*.—S-4-Mercapto-6-pyrimidylthiuronium chloride (1·5 g.) was heated under reflux for 1½ hours in N-sodium hydroxide (40 c.c.). After cooling, addition of dilute hydrochloric acid precipitated yellow plates (0·65 g., 68%). Recrystallisation from water gave 4 : 6-*dimercaptopyrimidine* as shining yellow prismatic needles which darkened above 230° and melted at 245—246° (decomp.) (Found : C, 33·6; H, 3·1; N, 19·4. $C_4H_4N_2S_2$ requires C, 33·4; H, 2·8; N, 19·4%). Ultra-violet absorption max. in aqueous solution at pH 6·98 : 214 ($\log_{10}\varepsilon = 3·92$), 260 (4·08), 283 (4·25), 248·5 mμ (4·53); at pH 13 : 268·5 (4·52), 316·5 mμ (4·44).

5-*Chloro*-2-*mercaptopyrimidime* (29).—2 : 5-Dichloropyrimidine (1·8 g.) and thiourea (1·0 g.) were heated under reflux in ethanol (40 c.c.) for 4½ hours, the colour of the solution slowly becoming yellow after the first hour. Evaporation nearly to dryness gave a mixture of the colourless thiuronium salt and the yellow mercapto-compound (2·7 g.). This was heated under reflux with N-sodium hydroxide (30 c.c.) for 1 hour. Cooling and acidification with dilute hydrochloric acid gave the product as a bright yellow powder (1·1 g., 61%). Sublimation at 140°/18 mm. gave pure 5-chloro-2-mercaptopyrimidine, m. p. 218° (decomp.) (Found : N, 19·2. Calc. for $C_4H_3N_2ClS$: N, 19·1%). English and Leffler (*J. Amer. Chem. Soc.*, 1950, **72**, 4324) report m. p. 222° (decomp.) for the compound prepared from 2 : 5-dichloropyrimidine and sodium hydrogen sulphide.

2-*Mercapto*-4 : 6-*dimethylpyrimidine*.—The pure compound was obtained by Hale and Williams's method (*ibid.*, 1915, **37**, 594). Sublimation at 130°/0·5 mm. gave a pale yellow powder, m. p. 209—210° (Hale and Williams report m. p. 210°).

2-*Mercapto*-4 : 6-*dimethylpyrimidine–Thiourea Complex*.—A solution of the mercaptopyrimidine (4·4 g.) in hot water (50 c.c.) was added to a solution of thiourea (2·4 g.) in hot water (30 c.c.), and the yellow solution rapidly filtered. As the solution cooled, highly refracting, bright yellow prisms separated (4·4 g., 65%), m. p. 196° (decomp.). Hale (*ibid.*, 1915, **37**, 1544) reports m. p. 192°.

Chromatography : (*a*) Ethyl acetate–water–acetic acid (3 : 2 : 1) as the solvent mixture, and 2½-inch wide Whatman filter paper strips. After drying, the strips were sprayed with ammoniacal silver nitrate, the position of the pyrimidine and thiourea being revealed by dark spots. The R_F values were : 2-mercapto-4 : 6-dimethylpyrimidine, 0·64; thiourea, 0·52; 2-mercapto-4 : 6-dimethylpyrimidine–thiourea complex, 0·63 and 0·53.

(*b*) Butanol (1 vol.) and water (1 vol.) as the solvent mixture. The R_F values were : 2-mercapto-4 : 6-dimethylpyrimidine, 0·61; thiourea, 0·32; 2-mercapto-4 : 6-dimethylpyrimidine–thiourea complex, 0·61 and 0·34.

Ultra-violet absorption max. in aqueous solution at pH 6·98 : 2-Mercapto-4 : 6-dimethylpyrimidine : 217·5 ($\log_{10}\varepsilon = 4·1$), 276 (4·38), 332 mμ (3·68). Thiourea : 235 mμ (4·04). 2-Mercapto-4 : 6-dimethylpyrimidine–thiourea complex : 217·5 (4·01), 235 (3·96), 276 (4·08); 332 mμ (3·41).

2-*Amino*-4 : 6-*dimethylpyrimidine–Urea Complex*.—This was prepared by the method of Bray, Lake, and Thorpe (*Biochem. J.*, 1951, **48**, 400).

Chromatography : The butanol–water mixture was used as the solvent. 2-Amino-4 : 6-dimethylpyrimidine could be detected as a dark spot on a fluorescent background when the paper strip was viewed by the light of a mercury-discharge lamp. Urea could be detected as a light spot on a dark background after the strip had been treated with ammoniacal silver nitrate, dried, and gently warmed. The R_F values were : 2-amino-4 : 6-dimethylpyrimidine, 0·80; urea, 0·27; 2-amino-4 : 6-dimethylpyrimidine–urea complex, 0·81 and 0·25.

2-*Amino*-4 : 6-*dimethylpyrimidine–Thiourea Complex*.—This was prepared as described for the urea complex. Recrystallisation from ethanol gave the *complex* as large colourless prisms, m. p. 159—160° (Found : C, 42·2; H, 6·45; N, 35·7; S, 16·3. $C_6H_9N_3,CH_4N_2S$ requires C, 42·3; H, 6·55; N, 35·2; 16·1%).

Chromatography : The butanol–water mixture was used as the solvent. The R_F values were : 2-amino-4 : 6-dimethylpyrimidine, 0·80; thiourea, 0·39; 2-amino-4 : 6-dimethylpyrimidine–thiourea complex, 0·38 and 0·79.

Physical Measurements.—The methods employed were described in Part II (preceding paper).

The authors thank Mr. M. Marshall for his assistance with some of the light absorption measurements and the Department of Scientific and Industrial Research for the award of a Maintenance Grant to one of them (M. P. V. B.).

THE UNIVERSITY, BRISTOL. [*Received, May 6th,* 1952.]

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714. *The Decomposition of Arylthiolsulphonic Acids. Identification of Thiolsulphonic and Sulphinic Acids as Benzylthiuronium Derivatives.*

By FREDERICK KURZER and J. ROY POWELL.

When liberated from their alkali salts with mineral acids, arylthiolsulphonic acids are rapidly decomposed into diarylsulphonyl trisulphide, aryl arylthiolsulphonate, and sulphur. A possible mechanism of this reaction is discussed. Both thiolsulphonic and sulphinic acids are conveniently characterised as benzylthiuronium salts.

ARYLTHIOLSULPHONIC acids are well known in the form of their salts, but are not stable in the free state. Blomstrand (*Ber.*, 1870, **3**, 963) and Otto and Tröger (*ibid.*, 1891, **24**, 492) reported that thiolsulphonic acids, when set free from their salts with mineral acids, decomposed almost immediately into the corresponding sulphinic acids and sulphur (equation 1), the latter giving rise to unspecified by-products; experimental details, however, were not given.

When postulating the intermediate formation of arylthiolsulphonic acids in a reaction involving arylthioureas, we (*J.*, 1950, 3269) referred to experiments on the decomposition of arylthiolsulphonic acids. The present paper records more detailed observations, arising from this work, on the instability of arylthiolsulphonic acids in strongly acid media.

When an arylthiolsulphonic acid was liberated from its salt under a variety of conditions, a diarylsulphonyl trisulphide, an aryl arylthiolsulphonate, and sulphur were obtained in approximately equivalent quantities. The addition of a large excess of hydrochloric acid to sodium toluene-*p*-thiolsulphonate, for example, produced an abundant precipitate, which was readily separated into ditoluene-*p*-sulphonyl trisulphide, *p*-tolyl toluene-*p*-thiolsulphonate, and sulphur. Varying small quantities of toluene-*p*-sulphinic acid were also formed. The same products resulted when the decomposition was carried out more slowly in stages. Comparable results were obtained with naphthalene-2-thiolsulphonic acid. The predominating reaction is satisfactorily represented by the overall equation (2) which agrees well with the observed yields of the individual products.

$$R{\cdot}SO_2{\cdot}SH \longrightarrow R{\cdot}SO_2H + S \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$4R{\cdot}SO_2{\cdot}SH \longrightarrow (R{\cdot}SO_2)_2S_3 + R{\cdot}SO_2{\cdot}SR + 2H_2O + S \quad . \quad . \quad . \quad (2)$$

Smaller concentrations of mineral acids also caused decomposition according to equation (2), but affected only part of the thiolsulphonic acid present, the remainder being unchanged. An aqueous solution of sodium toluene-*p*-thiolsulphonate, for example, when treated with 1 equiv. of hydrochloric acid and stored at room temperature for 12 hours, gave a mixture which, though acid to Congo-red, decomposed according to equation (2) to the extent of only 25—30%. The bulk of unchanged thiolsulphonic acid was readily recovered as the benzylthiuronium derivative. In the presence of a weak acid, such as acetic acid, the thiolsulphonate entity was stable on short heating to 100°; solutions of pH 3·8—3·4 remained unchanged indefinitely at room temperature. Free arylthiolsulphonic acids thus possess some stability, provided that the concentration of the added mineral acid is not excessive and temperatures are fairly low.

Since the decomposition of arylthiolsulphonic acids (equation 2) proceeds rapidly under appropriate conditions, a mechanism involving ionic species may be considered. The

experimental observations suggest that the thiolsulphonate ion is directly concerned in the reaction. Although a detailed mechanism cannot be decided upon with certainty, the following sequence of changes appears to account satisfactorily for the observed results:

$$3R{\cdot}SO_2{\cdot}SH \longrightarrow 3R{\cdot}SO_2H + 3S \quad . \quad . \quad .

large proportion of the sulphinic acid may be expected to disarrange according to equations (8) and (9) before all the theoretically possible trisulphide has been formed, the yields of which are consequently lowered.

Further support for the above mechanism was finally obtained as follows: if arylthiolsulphonate ions are directly concerned in the decomposition of aromatic thiolsulphonic acids, the interaction, in acid media, of 3 equivs. of sulphinic acid and 2 equivs. of sulphur in the presence of 1 equiv. of thiolsulphonic acid (*i.e.*, in the proportions suggested by equations 3—7) should produce higher yields of diarylsulphonyl trisulphide than the sum of the yields that are *independently* obtainable, *under identical conditions*, by (*a*) the reaction between 3 equivs. each of sulphinic acid and sulphur, and (*b*) the decomposition of 1 equiv. of thiolsulphonic acid. Experiments showed that this requirement was fulfilled.

The above results appear to support the view that the decomposition of arylthiolsulphonic acids is unlikely to consist of a complete preliminary fission into sulphinic acid and sulphur, followed by their recombination to the final products, but that the thiolsulphonate entity takes part directly in the reaction.

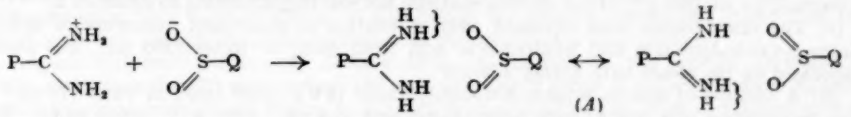
Of other alternative mechanisms, brief reference will only be made to the possible initial simultaneous ionisation of thiolsulphonic acids into thiolsulphonate and hydrogen ions on the one hand, and sulphonyl and hydrosulphide ions on the other. This dissociation, however, should produce hydrogen sulphide, of which at least small quantities might be expected to escape from the strongly acid media employed, before undergoing further reaction. Since no trace of this substance was observed in any of the decomposition experiments, the intermediate occurrence of hydrosulphide ions appears unlikely.

The above experiments—and other work now being carried out—made it desirable to have available a method which facilitated the isolation and identification of sulphinic acids, and more particularly thiolsulphonic acids, for which suitable derivatives appeared to be lacking. We have found their benzylthiuronium salts useful for this purpose. With one exception (*viz.*, *p*-fluorobenzenesulphinic acid; Hann, *J. Amer. Chem. Soc.*, 1935, **57**, 2167), the applicability of this method to the sulphinic and thiolsulphonic acid series has not been previously examined. The benzylthiuronium derivatives of a few typical representatives of the two series are therefore now described. They were readily prepared, in excellent yields, by the general procedure (Donleavy and Johnson, *Science*, 1923, **57**, 753; Donleavy, *J. Amer. Chem. Soc.*, 1936, **58**, 1004), which was equally applicable to aliphatic and aromatic sulphinic and thiolsulphonic acids.

Although this method makes it possible to recover the above acids in the form of highly crystalline derivatives, even from dilute solutions, the properties of the benzylthiuronium salts impose some limitations on their use. One disadvantage is the difficulty of recovering the original acids: acid hydrolysis converts the liberated sulphinic acids into the thiolsulphonate esters ($R{\cdot}SO_2{\cdot}SR$), whereas thiolsulphonic acids are decomposed according to equation (2); alkaline hydrolysis, on the other hand, produces the disagreeable toluene-ω-thiol as by-product. As previously observed with carboxylic acids, the m. p.s of the sulphinic acid derivatives fall within a small temperature range. Moreover, melting-point depressions due to admixture of different derivatives (particularly when the sulphinic acids concerned are of analogous structure) are sometimes small. In establishing the identity of a given specimen by mixed m. p. determination with authentic material, very close agreement between the m. p. and the mixed m. p. is therefore essential. The m. p.s of the benzylthiuronium derivatives of thiolsulphonic acids cover a wider range, and mixtures of these salts give rise to more distinct melting-point depressions.

Walker (*J.*, 1949, 1997) in discussing the power of compounds containing an unsubstituted amidino-group to form sparingly soluble salts with certain acids, has adduced reasons, on structural grounds, for the general observation that the m. p.s of benzylthiuronium salts of carboxylic acids cover only a small temperature range whereas those of sulphonic acid derivatives show a wider distribution. In view of the formal structural analogies of sulphinic and thiolsulphonic with carboxylic and sulphonic acids, respectively, it seems possible to explain the similar observations now made in the former two series, and to provide at the same time, further examples in support of the original hypothesis. Thus, following Walker's arguments (*loc. cit.*), the observed distribution of the m. p.s may

be accounted for, in the present case, by representing the benzylthiuronium salts of sulphinic acids by the resonance structure (*A*).



The aromatic thiolsulphonic acids required in this work were prepared by an improvement in the classical method (Spring, *Ber.*, 1874, **7**, 1158; Otto, *ibid.*, 1882, **15**, 127) by addition of a hot saturated solution of sulphur in acetone to aqueous sodium sulphinate, the former solvent being simultaneously removed under reduced pressure. In this way the uptake of the element was found to occur more readily than by simply stirring the sulphinate solution with sulphur. Owing to the limited solubility of sulphur in acetone, however, the procedure is most useful for the rapid preparation of small samples of thiolsulphonic acids. A second convenient method of preparing these acids, in the form of their pyridinium salts, consisted of the addition of sulphur to the pyridine solution of the corresponding sulphinic acid (cf. Kurzer, *J.*, 1950, 3269). Benzylthiuronium derivatives were directly obtained from the aqueous solutions of the pyridinium salts, thus confirming the general applicability of this synthesis of arylthiolsulphonic acids.

Another illustration of the usefulness of the benzylthiuronium derivatives may be given. The interaction of aromatic thioureas and sulphonyl chlorides has been shown (Kurzer, *loc. cit.*) to proceed by a mechanism involving the intermediate formation of unstable *S*-sulphonyl*iso*thioureas, which decompose into cyanamides and thiolsulphonic acids, but the occurrence of the latter products was only inferred indirectly. It has now been possible to isolate the intermediate thiolsulphonic acid in the form of its benzylthiuronium derivative. This test was again carried out with an *as*-disubstituted thiourea to avoid the complication of side reactions (*loc. cit.*): the products of the interaction of *as*-diphenylthiourea and toluene-*p*-sulphonyl chloride were *NN*-diphenylcyanamide and toluene-*p*-thiolsulphonic acid (equation 10). Additional more direct evidence for the mechanism previously suggested is thus provided.

$$\begin{aligned} Ph_2N{\cdot}CS{\cdot}NH_2 + R'{\cdot}SO_2Cl &\longrightarrow [Ph_2N{\cdot}C(S{\cdot}SO_2R'){:}NH] + HCl \\ &\longrightarrow Ph_2N{\cdot}CN + R'{\cdot}SO_2{\cdot}SH \quad . \quad . \quad . \quad (10) \end{aligned}$$

Experimental

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford. The yields of products obtained in the decomposition of arylthiolsulphonic acids are calculated on the basis of equation (2). Sodium toluene-*p*-sulphinate was employed in the form of the crystalline dihydrate throughout.

Decomposition of Toluene-p-*thiolsulphonic Acid.*—(i) To a solution of sodium toluene-*p*-thiolsulphonate dihydrate (7·4 g., 0·03 mole) in water (100 ml.) at 35°, an excess of concentrated hydrochloric acid (30 ml.) was added in one portion. A semicrystalline, almost white mass separated instantly, filling the whole volume of liquid. After 3 hours, the solid was filtered off and washed with water (filtrate: A), and the dried pale yellow powder (5·64 g.) extracted with boiling ethanol (2 × 20 ml.) (extracts: B). The residue (3·15 g.) was crystallised from benzene (50 ml.)–ethanol (10 ml.) and deposited minute, lustrous prisms of ditoluene-*p*-sulphonyl trisulphide, m. p. 184—186° (slight sintering at 160°) undepressed in admixture with authentic material (Found: C, 41·5; H, 3·5. Calc. for $C_{14}H_{14}O_4S_5$: C, 41·4; H, 3·5%). The mother-liquors therefrom deposited more trisulphide, m. p. 182—184° (total yield: 2·7 g., 88%), together with a few compact prisms of sulphur (0·15 g., 62%). The combined alcoholic extracts (B), evaporated to small volume (12 ml.) and decanted from a trace of insoluble material, deposited lustrous prisms of *p*-tolyl toluene-*p*-thiolsulphonate, m. p. 77—78° (total yield: 1·85 g., 88%).

The aqueous filtrate (A) was evaporated on the steam-bath to small volume and heated for 4 hours; it deposited a little oil, which solidified on cooling and consisted of *p*-tolyl toluene-*p*-thiolsulphonate, m. p. 76—78° (0·2 g.; accounting for 7% of the starting material *not* reacting according to equation 2). The aqueous filtrate therefrom, adjusted to pH 8 with sodium

hydroxide and treated with *S*-benzylthiuronium chloride (2·0 g.), gave the benzylthiuronium salt of toluene-*p*-sulphonic acid, m. p. 180—181° (undepressed by authentic material) (0·44 g.; accounting for another 2% of the starting material not reacting according to equation 2).

(ii) The same results were obtained when a solution of equivalent quantities of sodium toluene-*p*-thiolsulphonate and hydrochloric acid (0·03 mol.) in water (200 ml.) was slowly evaporated on the steam-bath during 3 hours.

(iii) A solution of sodium toluene-*p*-thiolsulphonate (4·9 g., 0·02 mole) in water (70 ml.) at room temperature was treated with hydrochloric acid (5·5 ml.; 10% w/v; 0·015 mol.). The liquid (which was acid to Congo-red) deposited, overnight, a pale yellow solid (A; 1·25 g.). The filtrate therefrom was treated with a saturated warm aqueous solution of *S*-benzylthiuronium chloride (4·0 g., 0·02 mole), giving a white crystalline precipitate (4·35 g., 62%) of the corresponding *derivative* of toluene-*p*-thiolsulphonic acid, m. p. 121—123° (from ethanol–light petroleum) (undepressed in admixture with material prepared as described below). Solid A, consisting of ditoluene-*p*-sulphonyl trisulphide, *p*-tolyl toluene-*p*-thiolsulphonate, and sulphur, was separated into its constituents as before; the yields corresponded to a conversion of 29% of the starting material according to equation (2).

Stability of Toluene-p-*thiolsulphonic Acid in Acetic Acid Solution* (*at* pH 3·6).—A solution of sodium toluene-*p*-thiolsulphonate (5·25 g., 0·025 mole) in water (100 ml.) was treated with acetic acid (2·25 g., 0·0375 mole), and a slight turbidity filtered off. The liquid (pH 3·40) was slowly evaporated nearly to dryness on the steam-bath; addition of water (200 ml.) gave once again a clear liquid (pH 3·58). One-half of this solution was treated with aqueous silver nitrate (2·55 g., 0·015 mole), yielding white semicrystalline silver toluene-*p*-thiolsulphonate (Found: C, 29·1; H, 2·6; Ag, 36·2. Calc. for $C_7H_7O_2S_2Ag$: C, 28·5; H, 2·4; Ag, 36·6%). The other half of the solution was made just alkaline to phenolphthalein with sodium hydroxide; addition, at 40°, of *S*-benzylthiuronium chloride (5·06 g., 0·025 mole) in water (10 ml.) and immediate removal of the crude oily product by decantation (to avoid contamination with the corresponding derivative of acetic acid which separates slowly on cooling) gave the benzylthiuronium derivative of toluene-*p*-thiolsulphonic acid, m. p. 121—123° (from ethanol–light petroleum) (undepressed in admixture with authentic material, prepared as described below.)

Storage of aqueous solutions of equimolecular proportions of sodium toluene-*p*-thiolsulphonate and acetic acid at 0° (for at least 6 months) caused no decomposition of the thiolsulphonic acid.

Decomposition of Naphthalene-2-thiolsulphonic Acid.—Addition of concentrated hydrochloric acid (10 ml.) to an aqueous solution of sodium naphthalene-2-thiolsulphonate (2·26 g., 0·008 mole) precipitated a pale yellow viscous material, which solidified on short storage. This was dissolved in boiling ethanol (4 × 12 ml.): the undissolved residue was sulphur (0·03 g., 47%). Fractional evaporation of the ethanolic extracts and repeated crystallisation from ethanol gave the less soluble dinaphthalene-2-sulphonyl trisulphide, m. p. 141—142° (slight sintering at 136°) [undepressed in admixture with material prepared by method of Tröger and Hornung (*J. pr. Chem.*, 1899, **60**, 113) who report m. p. 130—132°] (0·71 g., 74%) (Found: C, 49·7; H, 2·8. Calc. for $C_{20}H_{14}O_4S_5$: C, 50·2; H, 2·9%). The more soluble fraction gave 2-naphthyl napthalene-2-thiolsulphonate, m. p. 102—103° (0·36 g., 52%).

Interaction of Toluene-p-*sulphinic Acid and Sulphur.*—(i) Flowers of sulphur (0·35 g., 0·011 g.-atom) were suspended in a solution of sodium toluene-*p*-sulphinate (2·14 g., 0·01 mole) in hydrochloric acid (3N; 30 ml.) and the mixture stirred at 90—100° for 3 hours. The filtered solid (1·1 g.) consisted of ditoluene-*p*-sulphonyl trisulphide (0·15 g.), *p*-tolyl toluene-*p*-thiolsulphonate (0·40 g.), and unchanged sulphur. Prolonged stirring of the above reaction mixture at room temperature did not result in interaction to any measurable extent. Repeated evaporation of the mixture to small volume during 8 hours raised the yield of disulphonyl trisulphide (0·35 g.). Supplying the sulphur in the colloidal form by the addition of its saturated acetone solution (the solvent being simultaneously removed) did not substantially improve the yields of disulphonyl trisulphide (see below).

(ii) *In the presence of toluene*-p-*thiolsulphonic acid.* To hydrochloric acid (3N; 25 ml.), at 75°, a solution of sodium toluene-*p*-sulphinate (3·21 g., 0·015 mole) and sodium toluene-*p*-thiolsulphonate (1·23 g., 0·005 mole) in water (30 ml.), and a saturated boiling solution of sulphur (0·35 g., 0·011 g.-atom) in acetone, were slowly added side by side during 1 hour, the acetone being removed simultaneously under reduced pressure. The solidified product, separated as previously described, gave ditoluene-*p*-sulphonyl trisulphide (1·40 g., 70%) and *p*-tolyl toluene-*p*-thiolsulphonate (1·15 g., 82%).

A control experiment, carried out under identical conditions but in the absence of sodium

toluene-*p*-thiolsulphonate, gave only low yields of the trisulphide (0·14 g., 9%), much of the sulphinic acid being recovered unchanged (as the benzylthiuronium derivative; 2·9 g., 60%). (Since the quantity of sodium toluene-*p*-thiolsulphonate employed above would produce, independently, only approx. 0·50 g. of trisulphide, the present experiment shows that thiolsulphonate ions participate in the formation of the disulphonyl trisulphide.)

Arylthiolsulphonic Acids.—(a) *Sodium salts.* A solution of the sodium arylsulphinate (0·01 mole) in water (30 ml.)–acetone (20 ml.), to which 2 drops of aqueous sodium hydroxide had been added, was treated, during 1—2 hours, with a saturated solution of sulphur (0·011 g.-atom) in boiling acetone, the added solvent being simultaneously removed (at 40—45°) by distillation under reduced pressure. When all the sulphur had been added, the pale yellow liquid was diluted with more water (20 ml.), the acetone removed in a vacuum, and traces of unchanged sulphur removed by filtration with carbon. Evaporation in a vacuum-desiccator gave lustrous platelets of the sodium arylthiolsulphonate. For the preparation of benzylthiuronium derivatives the sodium salt solution was directly used.

(b) *Pyridinium salts.* A solution of the arylsulphinic acid (0·01 mole) in pyridine (12 ml.), treated with sulphur (0·011 g.-atom), was kept at 80° for 15 minutes, and poured into water (60 ml.). Traces of separated sulphur were removed by filtration with carbon. The resulting solutions of the pyridinium salt of arylthiolsulphonic acids in aqueous pyridine were directly used in preparing benzylthiuronium derivatives.

S-*Benzylthiuronium Derivatives of Acids.*—(i) *Sulphinic acids.* The well-stirred solution of the sodium sulphinate (0·01 mole) in water (80—100 ml.) was made acid (phenolphthalein) by dropwise addition of dilute hydrochloric acid. Separation of free sulphinic acid (in the case of the less soluble members of the series) was prevented by warming the solution gently if necessary. Addition of a warm (40°) saturated aqueous solution of *S*-benzylthiuronium chloride (3·0 g., 0·015 mole) gave immediately a crystalline precipitate of the *derivative*; the mixture was set aside at 0° for 2 hours, and the product filtered off and air-dried. Two or three crystallisations from ethanol–light petroleum (usual ratio 3 : 1) or from ethanol alone (in the case of the less soluble derivatives) gave the product, of constant m. p., in lustrous plates,

Benzylthiuronium derivatives of various sulphur acids.

Acid	M. p.	Yield,[1] %	Solvents [2] used and no. of recrystns.[3]	Formula of derivative	N, % : Found	N, % : Reqd.
Methanesulphinic	136—137°	50	III,[4] 3	$C_9H_{14}O_2N_2S_2$	11·3	11·4
Toluene-ω-sulphinic	152—153	60	II, 2	$C_{15}H_{18}O_2N_2S_2$	†	
Benzenesulphinic	154—155	85	I, 1	$C_{14}H_{16}O_2N_2S_2$	9·5	9·1
Toluene-*p*-sulphinic	167—168	84	I, 2	$C_{15}H_{18}O_2N_2S_2$	8·4	8·7 [5]
Toluene-*o*-sulphinic	178—179	90	I, 4	$C_{15}H_{18}O_2N_2S_2$	8·6	8·7
Naphthalene-2-sulphinic	168—169	76	II, 2	$C_{18}H_{18}O_2N_2S_2$	7·4	7·8
p-Bromobenzenesulphinic	171—172	60	II, 2	$C_{14}H_{15}O_2N_2S_2Br$	7·1	7·2
3 : 4-Dichlorobenzenesulphinic	170—171	90	II, 1	$C_{14}H_{14}O_2N_2S_2Cl_2$	7·2	7·4
Methanethiolsulphonic	141—142	52	III, 3	$C_9H_{14}O_2N_2S_3$	33·5	34·5 *
Benzenethiolsulphonic	91—93	77	III, 3	$C_{14}H_{16}O_2N_2S_3$	8·5	8·2
Toluene-*p*-thiolsulphonic	120—121	95	I, 3	$C_{15}H_{18}O_2N_2S_3$	7·4	7·9
Toluene-*o*-thiolsulphonic	137—138	66	II, 1	$C_{15}H_{18}O_2N_2S_3$	8·0	7·9
Naphthalene-2-thiolsulphonic	171—172	82	II, 3	$C_{18}H_{18}O_2N_2S_3$	23·9	24·6 *
p-Bromobenzenethiolsulphonic	146—147	73	II, 1	$C_{14}H_{15}O_2N_2S_3Br$	21·9	22·9 *
Methanesulphonic	148—149	63	I, 2	$C_9H_{14}O_3N_2S_2$	10·5	10·7

Note added in Proof.—Our attention has been drawn to the following three sulphinic acid derivatives prepared from other thiuronium chlorides: *p*-bromobenzylthiuronium salts of α-benzylthio-*p*-bromotoluene-α-sulphinic acid (m. p. 211°) and of the corresponding α-methylthio-acid (m. p. 220° [Snyder and Handrick, *J. Amer. Chem. Soc.*, 1944, **66**, 1860]; 1-naphthylmethylthiuronium salt of benzenesulphinic acid (m. p. 177°) [Bonner, *ibid.*, 1948, **70**, 3509].

* Analyses relate to sulphur.

† The derivative decomposed on storage, yielding benzaldehyde, and was not analysed.

[1] The yields of sulphinic acid derivatives are based on the quantity of sulphonyl chloride originally reduced to the sulphinic acid; those of thiolsulphonic acid derivatives are calculated from the quantity of sulphinic acid used in the conversion into the thiolsulphonic acid. [2] Solvents: (I) ethanol–light petroleum; (II) ethanol; (III) water, followed by crystallisation from ethanol–light petroleum. [3] The number of crystallisations required to give a product of constant m. p. is recorded. [4] Owing to its high solubility, this derivative was crystallised from fairly concentrated solution. [5] Found: C, 55·6; H, 5·9. $C_{15}H_{18}O_2N_2S_2$ requires C, 55·9; H, 5·6%.

usually freely soluble in warm acetone and ethanol, sparingly soluble in benzene, light petroleum, and cold water.

(ii) *Thiolsulphonic acids.* These derivatives were similarly prepared from the sodium or pyridinium salt solution of the thiolsulphonic acid (see above). The isolated product was usually crystallised once from hot (80°) water, and twice from ethanol–light petroleum (with the addition of a little charcoal to remove traces of separated colloidal sulphur, if necessary), giving lustrous plates of the *derivative*, of constant m. p. The solubilities resembled those under (i).

Interaction of as-*Diphenylthiourea and Toluene*-p-*sulphonyl Chloride: Isolation of Toluene*-p-*thiolsulphonic Acid.*—A solution of *as*-diphenylthiourea (3·40 g., 0·015 mole) in pyridine (15 ml.) was treated with toluene-*p*-sulphonyl chloride (2·90 g., 0·015 mole) and heated at 100° for 15 minutes. The liquid was stirred into ice-water (80 ml.) and acidified (to Congo-red) with concentrated acid. The supernatant aqueous layer was immediately decanted from the semi-solid deposit (A), treated with aqueous sodium hydroxide until just acid to litmus, and filtered with a little charcoal. Addition of *S*-benzylthiuronium chloride (3·05 g., 0·015 mole) and storage at 0° for several hours gave crystalline plates (m. p. 110—120°; 1·59 g., 30%); recrystallisation from ethanol–light petroleum yielded the benzylthiuronium derivative of toluene-*p*-thiolsulphonic acid, m. p. 121—123° (undepressed in admixture with authentic material). (Spontaneous evaporation, at room temperature, of the aqueous filtrates raised the yield to 42%.)

The solidified deposit (A) (2·2 g.) was *NN*-diphenylcyanamide, m. p. 70—72°, which was separated from small quantities of unchanged *as*-diphenylthiourea with cold acetone.

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715. *Effect of Methylation on the Light Absorption of Phenols. Part II.* Monophenylazophenols.*

By A. BURAWOY and J. T. CHAMBERLAIN.

The spectra of monophenylazophenols and of the corresponding nitrophenol derivatives are reported and compared with those of their methyl ethers. It is confirmed that the normal effect of methylation (in absence of hydrogen-bond formation and steric effects) is a displacement of the *B*- and *K*-bands to longer wave-lengths. The generally observed displacements to shorter wave-lengths may be due to a reversal of the effect of hydrogen-bond formation and also, in phenols substituted in the *ortho*-position, to reduced conjugation caused by intramolecular steric effects. The electronic spectra can serve as a test for the presence of an internal hydrogen bond in phenolic substances. The investigated *o*-hydroxyazo-compounds (I, III, IV) exist in solution as true phenols.

RECENTLY we reported an investigation of the effect of methylation on the absorption bands of phenols (Part I *). Whereas the normal effect of methylation (observed in hexane solution) is a displacement of the *B*- and *K*-bands to longer wave-lengths, in agreement with the greater electron-repelling power of the methyl group, displacements to shorter wave-lengths are generally observed. This is due partly to a reversal of the effect of hydrogen-bond formation involving the hydroxyl group (Morton and Stubbs, *J.*, 1940, 1347), and partly to a reduction of conjugation resulting from a repulsive interaction between the methoxyl group and substituents in the *ortho*-position.

We have extended this investigation to monophenylazophenols of the benzene series. In order to eliminate any difficulty arising from the hitherto uncertain structure of these

* Part I, *J.*, 1952, 2310.

substances, the spectra of the corresponding nitrophenols and their methyl ethers have been compared.

The data for the *B*- and *K*-bands of 4-methyl-2-phenylazophenol (I), *p*-phenylazophenol (II), and 4-phenylazoresorcinol (III), as well as of 2- and 4-nitrophenol (VI and VII), 4-nitroresorcinol (VIII), and their methyl ethers, in alcoholic solution, are listed in Table 1, together with those of the azo-compounds in hexane and chloroform solution (for method used, see Part I, *loc. cit.*).

TABLE 1.

			Phenol		Methyl ether	
Compound	Solvent	Band	λ, max.	$10^3\varepsilon$, max.	λ, max.	$10^3\varepsilon$, max.
I	C_6H_{14}	*B*	3935	9·8	3590	9·0
		K	3230	25·0	3090	13·5
	$CHCl_3$	*B*	3940	9·0	3615	8·5
		K	3240	24·0	3120	12·5
	EtOH	*B*	3935	9·6	3600	8·4
		K	3235	25·0	3110	12·5
II	C_6H_{14}	*K*	3365	28·5	3380	24·7 †
	$CHCl_3$	*K*	3480	28·5	—	—
	EtOH	*K*	3510	29·0	3415	24·0 †
III	C_6H_{14}	*K*	3680	23·0	—	—
	$CHCl_3$	*K*	3765	26·0	—	—
	EtOH	*K*	3800	26·0	—	—
IV	C_6H_{14}	*K*	3765	23·0	3590	17·0
	$CHCl_3$	*K*	3740	24·0	3625	19·0
	EtOH	*K*	3745	25·0	3617	19·0
V	C_6H_{14}	*K*	3565	23·0	3590	17·0
	$CHCl_3$	*K*	3690	23·0	3625	19·0
	EtOH	*K*	3720	24·0	3617	19·0
VI	,,	*B*	3435	3·6 *	3172	2·85 *
		K	2730	6·6	2585	3·45
VII	,,	*K*	3140	13·0 *	3050	13·0 *
VIII	,,	*K*	3450	14·0	—	—
IX	,,	*K*	3345	10·5	3225	8·0
X	,,	*K*	3295	9·5	3225	8·0

(I) = 4-Methyl-2-phenylazophenol. (VI) = *o*-Nitrophenol.
(II) = *p*-Phenylazophenol. (VII) = *p*- ,,
(III) = 4-Phenylazoresorcinol. (VIII) = 4-Nitroresorcinol.
(IV) = 4- ,, 1-methyl ether. IX) = 4- ,, 1-methyl ether.
(V) = 4- ,, 3- ,, (X) = 4- ,, 3- ,,

* Part I. † Burawoy, *J.*, 1937, 1865.

Analysis of Spectra.—The spectrum of azobenzene in hexane (Burawoy, *J.*, 1937, 1865) shows in addition to the characteristic low-intensity *R*-band of the azo-group (λ 4480 Å; ε 425) a *K*-band of high intensity (λ 3130 Å; ε 20,000) due to an electronic transition along the conjugated system Ph·N=NPh (Fig. 1). The *B*(enzene)-band is not observed, being masked by the *K*-band. Similarly, nitrobenzene in alcohol exhibits the *K*-band (λ 2590 Å; ε 9500) associated with the conjugated system O=NO·Ph (Fig. 2), in addition to a broad inflexion of low intensity (cf. Scheibe, *Ber.*, 1926, **59**, 2622).

Examination of the spectra of the monophenylazophenols (I—III) in hexane (Fig. 1) and the nitrophenols (VI—VIII) in alcohol (Fig. 2) reveals that the *K*-band is displaced appreciably to longer wave-lengths by a terminal (*p*-)hydroxyl group, whereas the effect of a hydroxyl group in the branching *ortho*-position is only slight (cf. Burawoy, *Ber.*, 1930, **63**, 3155; *J.*, 1937, 1865; 1939, 1177).

4-Methyl-2-phenylazophenol (I) and *o*-nitrophenol (VI) also show the *B*-band of lower intensity at longer wave-lengths which in the spectra of *p*-phenylazophenol (II), 4-phenylazoresorcinol (III), and the corresponding nitrophenols (VII and VIII) is again masked by the *K*-band of higher intensity. Its presence in the spectrum of (III) in a position similar to that observed for (I) is clearly indicated by a considerable extension of the *K*-band to longer wave-lengths. Thus, in contrast to the *K*-bands the (masked) *B*-bands of azo-

benzene and nitrobenzene are displaced to considerably longer wave-lengths by a hydroxyl group in the *ortho*-position and not at all by a hydroxyl group in the *para*-position.

The *R*-band of the azo-group is also observed in the spectrum of *p*-phenylazophenol in hexane solution (λ 4410 Å; ε 780), but is completely masked by the *B*-band in the spectra of 4-methyl-2-phenylazophenol and 4-phenylazoresorcinol.

Effect of Methylation on B- and K-*Bands.*—Methylation of a hydroxyl group in the *para*-position to the azo-group in (II), (III), and (V) is responsible in hexane for a slight shift of the *K*-band to longer, but in chloroform and alcohol to shorter, wave-lengths (<100 Å) and for a slight change of intensity (Figs. 3—8). Obviously, the position of the *K*-bands is much more dependent on the solvent in the spectra of the phenols than in those of their methyl ethers. This lends additional support to the view that the normal effect of methylation (in hexane) is a displacement to longer wave-lengths and that the observed shifts to shorter wave-lengths are due to a reversal of the bathochromic effect of hydrogen bond formation involving the solvent (solvation). The corresponding nitrophenols (VII), (VIII), and (X) and their methyl ethers in alcoholic solution show analogous spectral relations (Figs. 4, 6, 8).

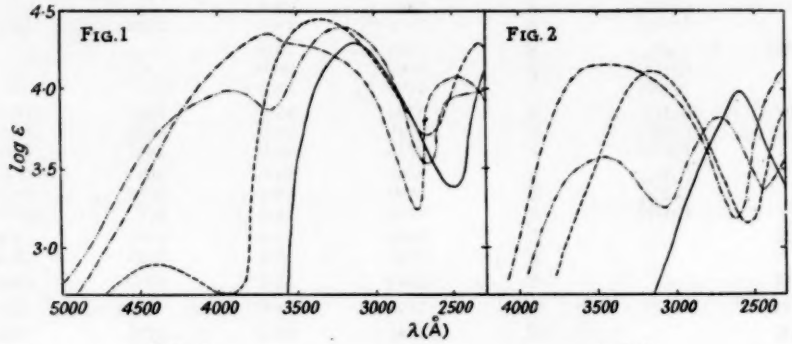


FIG. 1.

——— *Azobenzene.*
— — — 4-*Phenylazophenol.*
— · · · — 4-*Methyl-2-phenylazophenol.*
— · — · 4-*Phenylazoresorcinol in hexane.*

FIG. 2.

——— *Nitrobenzene.*
— — — 4-*Nitrophenol.*
— · · · — 2-*Nitrophenol.*
— · — · 4-*Nitroresorcinol in alcohol.*

On the other hand, methylation of a hydroxyl group in the *ortho*-position to the azo-group in (I), (III), and (IV) results in a more considerable displacement of the *K*-bands to shorter wave-lengths in all three solvents (100—200 Å). The effect of solvents on the position of the bands of both the phenols and their methyl ethers is very similar. Again, analogous effects are observed for the corresponding nitrophenol derivatives (VI), (VIII), and (IX) in alcoholic solution (Figs. 9—14). Two factors appear to contribute to these spectral changes.

(i) A reversal of the bathochromic effect of the internal hydrogen bond, known to be present in these substances (cf. Hendricks, Wulf, Hilbert, and Liddel, *J. Amer. Chem. Soc.*, 1936, **58**, 1991; Burawoy and Markowitsch-Burawoy, *J.*, 1936, 36). This contribution is comparatively small. Thus, the methylation of salicylaldehyde displaces the *K*-band in hexane and alcohol by 85 and 20 Å respectively to shorter wave-lengths, the intensity being also only slightly changed (cf. XI, Table 2). We have ascertained that this effect is not associated with the presence in itself of a hydroxyl group in the *ortho*-position. As already noted by Friedel, Orchin, and Reggel (*ibid.*, 1948, **70**, 199), the displacement of the *K*-band in hexane solution of 2-hydroxydiphenyl, which does not contain an internal hydrogen bond, is normal, *i.e.*, to longer wave-lengths on methylation (cf. XII, Table 2). Undoubtedly, a comparison of the spectra of a phenol and its methyl ether in hexane provides a method for the detection of an internal hydrogen bond.

(ii) A steric repulsion between the nitro-group or azo-group and the oxygen atom of

the methoxyl group in the *ortho*-position, which accounts for the considerably greater displacements to shorter wave-lengths of the *K*-bands on methylation of the 4-nitro- and 4-phenylazoresorcinols and their 1-methyl ethers as well as of *o*-nitrophenol and 4-methyl-

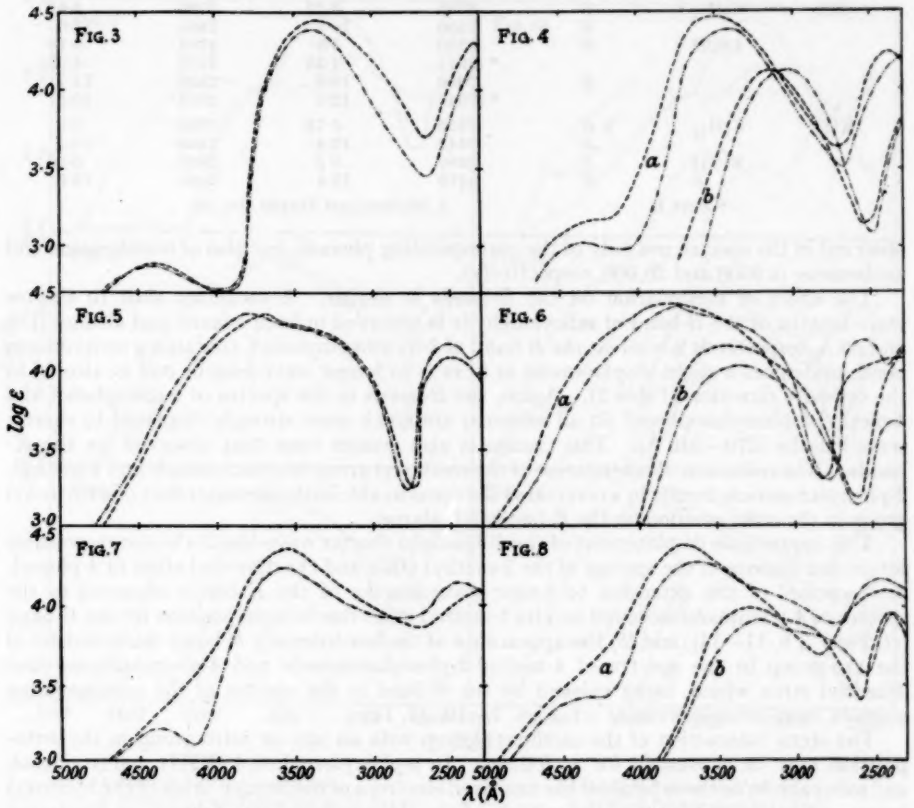


FIG. 3.

——— 4-*Phenylazophenol.*
— · · — 4-*Phenylazoanisole in hexane.*

FIG. 4.

a ——— 4-*Phenylazophenol.*
a — · · — 4-*Phenylazoanisole.*
b ——— 4-*Nitrophenol.*
b — · · — 4-*Nitroanisole in alcohol.*

FIG. 5.

——— 4-*Phenylazoresorcinol.*
— · · — 4-*Phenylazoresorcinol* 1-*methyl ether in hexane.*

FIG. 6.

a ——— 4-*Phenylazoresorcinol.*
a — · · — 4-*Phenylazoresorcinol* 1-*methyl ether.*
b ——— 4-*Nitroresorcinol.*
b — · · — 4-*Nitroresorcinol* 1-*methyl ether in alcohol.*

FIG. 7.

——— 4-*Phenylazoresorcinol* 3-*methyl ether.*
— · · — 4-*Phenylazoresorcinol dimethyl ether in hexane.*

FIG. 8.

a ——— 4-*Phenylazoresorcinol* 3-*methyl ether.*
a — · · — 4-*Phenylazoresorcinol dimethyl ether.*
b ——— 4-*Nitroresorcinol* 3-*methyl ether.*
b — · · — 4-*Nitroresorcinol dimethyl ether in alcohol.*

2-phenylazophenol. The resulting reduction of conjugation of these groups is clearly shown by the intensities of the *K*-bands in the spectra of *o*-nitroanisole and 4-methyl-2-phenylazoanisole (ε 3450 and 13,500, respectively) which are considerably lower than those

TABLE 2.

Compound	Solvent	Band	Phenol λ, max.	Phenol $10^{3}\varepsilon$, max.	Methyl ether λ, max.	Methyl ether $10^{3}\varepsilon$, max.
(XI)	C_6H_{14} †	*B*	3285	3·23	3100	5·62
		K	2550	10·0	2465	12·0
	EtOH †	*B*	3250	3·0	3195	4·26
			* (3244	4·35	3210	4·55)
		K	2550	10·0	2530	11·7
			* (2540	12·5	2528	10·5)
(XII)	C_6H_{14}	*B*	2825	5·75	2835	6·2
		K	2442	12·5	2460	15·5
	EtOH	*B*	2880	5·5	2850	5·50
		K	2470	13·5	2464	13·0

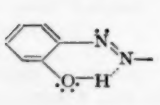
* Part I. † Morton and Stubbs, *loc. cit.*

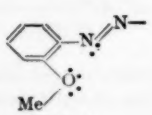
observed in the spectra not only of the corresponding phenols, but also of nitrobenzene and azobenzene (ε 9500 and 20,000, respectively).

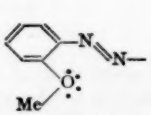
The effect of methylation on the *B*-bands is similar. A moderate shift to shorter wave-lengths of the *B*-band of salicyaldehyde is observed in both hexane and alcohol (185 and 55 Å, respectively), whereas the *B*-band of 2-hydroxydiphenyl, containing no hydrogen bond, undergoes a slight displacement in hexane to longer wave-lengths and in alcohol in the opposite direction (Table 2). Again, the *B*-bands in the spectra of *o*-nitrophenol and 4-methyl-2-phenylazophenol (in all solvents) are much more strongly displaced to shorter wave-lengths (270—340 Å). This change is also greater than that observed for the *K*-bands. The reduction of conjugation of the methoxyl group in *o*-nitroanisole and 4-methyl-2-phenylazoanisole results in a reversal of the considerable bathochromic effect of a hydroxyl group in the *ortho*-position on the *B*-bands (cf. above).

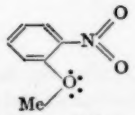
This appreciable displacement of the *B*-bands to shorter wave-lengths is also responsible for (*a*) the absence in the spectra of the 3-methyl ether and the dimethyl ether of 4-phenylazoresorcinol of the extension to longer wave-lengths of the *K*-bands observed in the spectra of 4-phenylazoresorcinol and its 1-methyl ether due to superposition by the *B*-band (cf. Figs. 7, 8, 11—14), and (*b*) the appearance of the low-intensity *R*-band characteristic of the azo-group in the spectra of 4-methyl-2-phenylazoanisole and 4-phenylazoresorcinol dimethyl ether which, being masked by the *B*-band in the spectra of the corresponding phenols, now becomes evident (cf. Figs. 7—10, 13, 14).

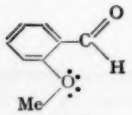
The steric interaction of the methoxyl group with an azo- or nitro-group in the *ortho*-position may be accounted for as follows. In *o*-phenylazophenol (XIII), *o*-nitrophenol, and salicyaldehyde the orbitals of the unshared electrons of the oxygen atom of the hydroxyl group will extend (mainly) to the outside of the six-membered ring formed, as illustrated for (XIII). Their steric repulsive interaction with the unshared electrons of the nitrogen atom of the azo-group (also extending outwards), or the electrons of the N=O and C–H linkages respectively, will be at a minimum. On the other hand, for steric reasons the most stable configurations of the methyl ethers are probably as shown in (XIV)—(XVI), in which the orbitals of the oxygen atom of the methoxyl group extend inwards and are involved in appreciable steric repulsion with the unshared electrons of the nitrogen atom in (XIV*a*) or the electrons of the N=N or N=O linkage in (XIV*b*) and (XV) respectively, whereas in *o*-methoxybenzaldehyde (XVI) repulsion with the C–H linkage will be too small to allow unambiguous spectroscopic detection. Finally, the most stable configurations of both 2-hydroxydiphenyl and its methyl ether being undoubtedly similar, methylation is not responsible for an (enhanced) steric effect, in agreement with the negligible displacements observed for both the *B*- and *K*-bands.


(XIII)


(XIV*a*)


(XIV*b*)


(XV)


(XVI)

Structure of o-Hydroxyazobenzenes.—Numerous investigations have been carried out to elucidate the structure of *o*-hydroxyazo-compounds which may be true phenols or *o*-quinone phenylhydrazones. Burawoy and Markowitsch (*Annalen*, 1933, **504**, 180), having un-

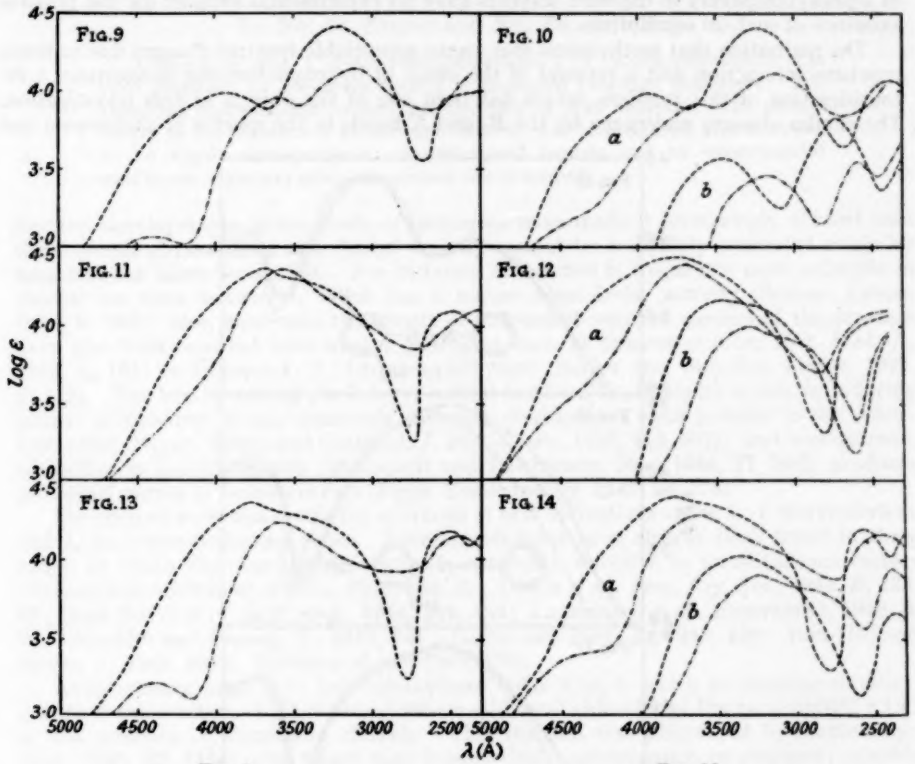


Fig. 9.

— — — 4-*Methyl-2-phenylazophenol.*
— · — 4-*Methyl-2-phenylazoanisole in hexane.*

Fig. 10.

a — — — 4-*Methyl-2-phenylazophenol.*
a — · — 4-*Methyl-2-phenylazoanisole.*
b — — — 2-*Nitrophenol.*
b — · — 2-*Nitroanisole in alcohol.*

Fig. 11.

— — — 4-*Phenylazoresorcinol.*
— · — 4-*Phenylazoresorcinol* 3-*methyl ether in hexane.*

Fig. 12.

a — — — 4-*Phenylazoresorcinol.*
a — · — 4-*Phenylazoresorcinol* 3-*methyl ether.*
b — — — 4-*Nitroresorcinol.*
b — · — 4-*Nitroresorcinol* 3-*methyl ether in alcohol.*

Fig. 13.

— — — 4-*Phenylazoresorcinol* 1-*methyl ether.*
— · — 4-*Phenylazoresorcinol dimethyl ether in hexane.*

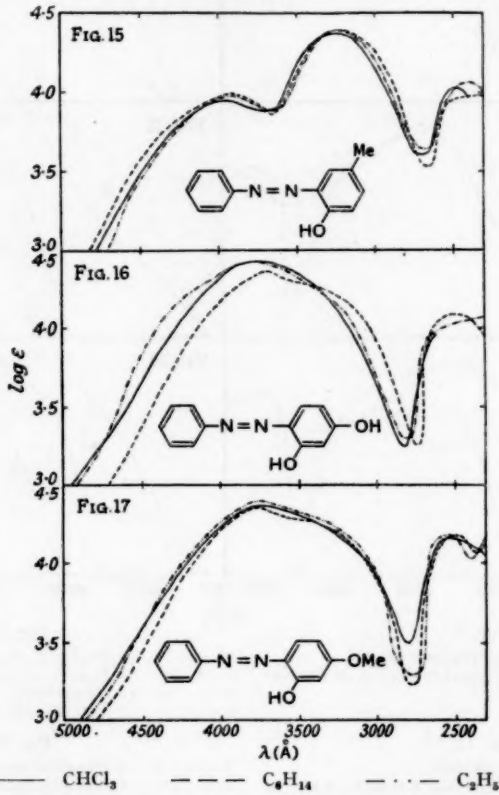
Fig. 14.

a — — — 4-*Phenylazoresorcinol* 1-*methyl ether.*
a — · — 4-*Phenylazoresorcinol dimethyl ether.*
b — — — 4-*Nitroresorcinol* 1-*methyl ether.*
b — · — 4-*Nitroresorcinol dimethyl ether in alcohol.*

ambiguously shown that 1-phenylazo-2-naphthol and 2-phenylazo-1-naphthol are present in solution as β-naphthaquinone phenylhydrazones, observed that the spectra of *o*-phenylazophenol and its methyl ether show differences which are considerably greater than could be expected at that time for true phenols. It was concluded that *o*-phenylazophenol also exists in solution as *o*-benzoquinone phenylhydrazone. Kuhn and Bär (*ibid.*, 1935, **516**, 73) questioned this interpretation, believing that the band of lower intensity at longer

wave-lengths in the spectrum of this substance might indicate the existence of an equilibrium. Burawoy (*ibid.*, 1936, **521**, 298) maintained the original view, pointing out that this is a *B*(enzene)-band also observed in *o*-benzoquinone, and that the very similar spectra of *o*-phenylazophenol in different solvents gave no experimental support for the possible existence of such an equilibrium.

The realisation that methylation may cause appreciable spectral changes due to steric repulsive interaction and a reversal of the effect of hydrogen-bonding necessitates a reconsideration of this problem, which has been one of the objects of this investigation. The similar changes undergone by the *B*- and *K*-bands in the spectra of azobenzene and



nitrobenzene on introduction of a hydroxyl group in the *ortho*-position and on its methylation show that the examined *o*-hydroxyazo-compounds exist in solution as true phenols. The spectral changes observed on methylation are not due to a qualitative change of structure and, as already pointed out by Burawoy and Markowitsch-Burawoy (*J.*, 1936, 36), cannot be reconciled with an interpretation of the internal hydrogen bond present by resonance hybrids involving both the azo- and the phenol structures (for similar conclusions reached more recently with regard to the related problems of the structure of the porphyrins and tropolones, see Erdman and Corwin, *J. Amer. Chem. Soc.*, 1946, **68**, 1886; Cook, Gibb, Raphael, and Somerville, *J.*, 1951, 508). Moreover, the very small variations of the spectra of (I), (III), and (IV) in different solvents (Figs. 15—17) do not give any experimental indication of tautomeric equilibria, the existence of which in more complicated *o*-hydroxyazo-compounds will, however, be shown elsewhere (cf. Burawoy, Salem, and Thompson, *Chem. and Ind.*, 1952, 410).

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716. *Potential Chemical Pituitary Inhibitors of the Polyarylethylene Series.*

By Ng. D. Xuong and Ng. Ph. Buu-Hoï.

A series of new 1 : 1-diarylethylenes and 1 : 1 : 2-triarylethylenes has been prepared for biological testing as potential pituitary inhibitors. The abnormal condensation to polyarylethylenes of acid chlorides with phenyl ethers, in the presence of aluminium chloride, was investigated, and is shown to be highly susceptible to constitutional factors and to experimental conditions. Certain other compounds are described.

Recent developments in the study of œstrogens have made it increasingly evident that their overall physiological and clinical activity cannot be accurately estimated solely by means of the Allen–Doisy test. For instance, stilbœstrol is frequently more valuable in clinical use than hexœstrol, which has a higher Allen–Doisy activity (Bishop, *Lancet*, 1948, ii, 764); also, successful treatments of stilbœstrol-resistant cancers of the prostate have also been reported with weaker œstrogens such as dienœstrol (Cox, *Brit. Med. J.*, 1946, ii, 191) or 1-bromo-1 : 2 : 2-triphenylethylene (Berger and Buu-Hoï, *Lancet*, 1947, ii, 173). Further, in animal physiology, œstriol has been found highly active in inducing œstrus in immature female mammals, although displaying a weak potency in the Allen–Doisy test (Meyer, Miller, and Cartland, *J. Biol. Chem.*, 1936, **112**, 597); and lumiœstrone, ineffective in spayed animals (Butenandt and Poschmann, *Ber.*, 1944, **77**, 392), produces prolonged œstrus in immature rats (Figge, *Endocrinology*, 1945, **36**, 178).

The present work deals with the synthesis of new derivatives of the 1 : 1-diarylethylene and 1 : 1 : 2-triarylethylene series. Several œstrogens have already been found in these series, in which the œstrogenic activity is extremely sensitive to constitutional factors (Robson and Schönberg, *Nature*, 1942, **150**, 22; Dodds *et al.*, *Proc. Roy. Soc.*, 1944, *B*, **132**, 83; Buu-Hoï *et al.*, *Compt. rend.*, 1944, **219**, 589; Lacassagne *et al.*, *Experientia*, 1946, **2**, 70; Buu-Hoï and Lecocq, *J.*, 1947, 641; Carter and Hey, *J.*, 1948, 150; Buu-Hoï and Royer, *J.*, 1948, 1078; Tadros *et al.*, *J.*, 1949, 439).

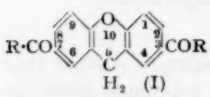
An interesting route to 1 : 1-diarylethylenes, $CRR'{:}CAr_2$ in which Ar contains alkyloxy-groups is the reaction of alkyl phenyl ethers with acid chlorides of the type $CHRR'{\cdot}COCl$ in the presence of aluminium chloride. This reaction was discovered by Gattermann (*Ber.*, 1889, **22**, 1130), who found that Friedel–Crafts condensation of propionyl chloride with anisole yielded 1 : 1-di-*p*-methoxyphenylpropene in addition to 4-methoxypropiophenone, the normal product. Later, it was extended by Skraup and Nieten (*Ber.*, 1924, **57**, 1300) to the preparation of 1 : 1-di-*p*-methoxyphenyl-*n*-butene, and its mechanism was studied by Mentzer and Xuong (*Compt. rend.*, 1946, **222**, 1004; XIth International Congress of Chemistry, London, 1947). This reaction has now been applied to a series of alkyl ethers of mono- and di-hydric phenols on the one hand, and to several acid chlorides on the other. Formation of 1 : 1-diarylethylenes was favoured by use of an excess of the phenyl ether, and hindered when the reaction was performed in certain solvents such as nitrobenzene, or involved highly reactive phenol ethers. A series of reactions effected without solvent, and affording several new 1 : 1-diarylethylenes, is given in Table 1*a* (p. 3742), where references are also given to other preparations by this method.

The influence of constitutional factors is shown in Table 2, which lists the results of standardised Friedel–Crafts reactions between propionyl chloride and various phenyl and thiophenyl ethers.

The abnormal Gattermann reaction can also be applied to the synthesis of symmetrically substituted 1 : 1 : 2-triarylethylenes (Mentzer and Xuong, *loc. cit.*; Xuong, Cagniant, and Mentzer, *Compt. rend.*, 1948, **226**, 1453), and was here used for the preparation of 1 : 1-di-(4-methoxy-2-methylphenyl)- and 1 : 1-di-(3-chloro-4-methoxyphenyl)-2-phenylethylene from phenylacetyl chloride and the methyl ethers of *o*-chlorophenol and *m*-cresol. Methyl or halogen groups were introduced in order to decrease the œstrogenic properties of these triarylethylenes. We have also prepared 1-*p*-*n*-propylphenyl- and 1-*p*-*n*-butylphenyl-1 : 2-

diphenylethylene by routine Grignard reactions of benzylmagnesium chloride on 4-*n*-propyl- and 4-*n*-butyl-benzophenone, and dehydration of the alcohols thus formed. Bromination of the four 1 : 1 : 2-triarylethylenes mentioned readily yielded the corresponding 1 : 1 : 2-triaryl-2-bromoethylenes. It is noteworthy that 1 : 1-di-*p*-methoxyphenyl-propene and -butene could also be converted by bromine into the corresponding 2-bromo-derivatives (cf. Gattermann, *loc. cit.*; Wieland, *Ber.*, 1910, **43**, 718; Lipp, *Ber.*, 1923, **56**, 569).

During this work it was observed that xanthen, which can be considered as a phenyl ether, underwent Friedel–Crafts reactions with acetyl and propionyl chloride to give 3 : 7-diacetyl- (I; R = Me) and 3 : 7-dipropionyl-xanthen (I; R = Et) as the main products, no corresponding ethylenic compounds being detected. Incidentally, a series of new ketones derived from *n*-propylbenzene was prepared (see Table 3).



(I)

The 1 : 1-diaryl- and 1 : 1 : 2-triaryl-ethylenes described, which are non-œstrogenic or only feebly so, are being tested for potential pituitary-inhibiting activity; results will be reported elsewhere.

Experimental

The solvent for recrystallisation was methanol, unless stated otherwise.

Abnormal Gattermann Reactions.—(a) *Without solvent.* To a solution of the redistilled acid chloride (1 mol.) in the phenyl ether (2·5—3 mol.) containing phosphorus oxychloride (*ca.* 1 c.c.), finely powdered aluminium chloride (1·5—2 mol.) was added in small portions with stirring.

Table 1*a*.

No.	Phenyl ether, H·Ar: Ar =	Acid chloride, CHRR′·COCl: R	R′	1 : 1-Diarylethylene, CRR′:CAr$_2$: M. p.*	B. p./mm.	Formula	Found, %: C	H	Reqd., %: C	H
1	C_6H_4·OMe	Me	Me	66°	*ca.* 215°/12	$C_{18}H_{20}O_2$	80·5	7·5	80·6	7·5
2	C_6H_4·OMe	H	Pr^i	—	220/13	$C_{19}H_{22}O_2$	80·6	7·5	80·9	7·8
3	C_6H_4·OEt	H	Et	75	240/12	$C_{20}H_{24}O_2$	81·0	8·1	81·1	8·1
4	C_6H_4·OEt	H	Pr^i	—	235/13	$C_{21}H_{26}O_2$	80·9	8·1	81·3	8·4
5	C_6H_4·OBu^n	H	Me	49	280—285/22	$C_{23}H_{30}O_2$	81·4	9·0	81·7	8·9
6	*o*-C_6H_3Me·OMe	H	Me	93 [a]	224—225/13	$C_{19}H_{22}O_2$	80·5	8·0	80·8	7·8
7	*m*-C_6H_3Me·OMe	H	Me	92 [b]	220/13	,,	80·4	7·6	,,	,,
8	*m*-C_6H_3Me·OEt	H	Me	—	238—240/13 [b]	$C_{21}H_{26}O_2$	81·0	8·6	81·3	8·4
9	*o*-$C_6H_3(OMe)_2$	H	Me	81 [b] †	265—268/12	—	—	—	—	—
10	*m*-$C_6H_3(OMe)_2$	H	Me	89	—	$C_{19}H_{22}O_4$	72·4	7·1	72·6	7·0

* Where a m. p. is not given, the substance was a liquid.
† Prepared by another method by Haworth, Mavin, and Sheldrick (*J.*, 1934, 1423).
[a] Yield, 55%. [b] Yield, 50%.

Analogous compounds have been prepared from anisole and/or phenetole and lower aliphatic acid chlorides and/or mono- or di-chloroacetyl chloride by Gattermann (*Ber.*, 1889, **22**, 1132), Weill (*Bull. Soc. chim.*, 1931, **49**, 1811), Wiechell (*Annalen*, 1894, **279**, 338), Fritsch and Feldmann (*ibid.*, 1899, **308**, 78), and Brand (*Ber.*, 1913, **46**, 2942).

Table 1*b*.

No.	Phenones, CHRR′·COAr: M. p.	B. p./mm.	Derivative, and m. p.
1	—	280°/760	Semicarbazone, 208°
2	—	178/13	,, 210
3	42°	168/12	(See Klages, *Ber.*, 1904, **37**, 4001)
4	—	178/12	Semicarbazone, 192
6	42	—	Oxime, 99 (see *idem*, *ibid.*, p. 3991)
7	—	—	,, 95 ,, ,,

The mixture was kept for 72 hours at room temperature and decomposed with cold dilute hydrochloric acid, the organic layer taken up in ether, and the ethereal solution washed with a 5% aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). After removal of the solvent, the residue was fractionated in a vacuum. The ethylene fraction boiled at least 40° higher than the normal ketonic reaction product; in most cases, it could be recrystallised from ethanol or ligroin, and the colourless solid obtained gave with sulphuric acid deep halochromic colours, ranging from orange-red to deep violet. The 1 : 1-*diarylethylenes* are recorded in

Table 1*a*. The reactions giving rise to them are numbered, and these numbers are used in Table 1*b* to denote the corresponding, usually predominating, ketonic products.

(b) *With solvent.* A solution of the acid chloride (1·1 mol.) and the phenyl ether (1 mol.) in pure benzene or nitrobenzene (4 parts) was treated with aluminium chloride (1·5 mol.) as above; after 18 hours at room temperature, the mixture was decomposd with ice and hydrochloric acid, the solvent removed by steam-distillation, and the residue treated in the usual way. The results are recorded in Table 2.

TABLE 2. *Yields of reaction with propionyl chloride.*

Phenyl ether	Solvent *	Yield of 1 : 1-diarylethylene, % †	Phenyl ether	Solvent *	Yield of 1 : 1-diarylethylene, % †
Anisole	B	60—70	Methyl thymyl ether	N	0
Anisole	N	30—40	*p*-Xylyl 2-methyl ether	B	0
Phenetole	B	30—40	" "	B	0
n-Butoxybenzene	B	30—40	1-Methoxynaphthalene	N	0
Diphenyl ether	B	20—25	2-Methoxynaphthalene	N	0
Thioanisole	N	20—25	Veratrole	N	0
Methyl thymyl ether	B	0	1 : 3-Dimethoxybenzene	N	0

* B = Benzene. N = nitrobenzene.

† Under the experimental conditions used, yields below 10% could not be determined with accuracy, and the zero values are nominal. The yields were calculated with reference to the ether.

The main product from the reaction (5) of propionyl chloride upon *n*-butoxybenzene was 4-n-*butoxypropiophenone*, a pale yellow oil, b. p. 199—200°/32 mm., solidifying to large shiny colourless plates, m. p. 29° (Found: C, 75·6; H, 8·7. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·7%); it was characterised by formation of a phenylhydrazone, which was converted by hydrogen chloride in acetic acid into 2-p-n-*butoxyphenyl*-3-*methylindole*, fine shiny colourless prisms, m. p. 98°, giving an orange colour with sulphuric acid (Found: C, 81·5; H, 7·3. $C_{19}H_{21}ON$ requires C, 81·7; H, 7·5%); the same ketone (5 g.) yielded with isatin (4·8 g.) and potassium hydroxide (5 g.) in ethanol medium (24 hours' refluxing) 2-p-n-*butoxyphenyl*-3-*methylcinchoninic acid*, crystallising from acetic acid as fine yellowish prisms, m. p. 275° (Found: N, 4·2. $C_{21}H_{21}O_3N$ requires N, 4·1%); a similar Pfitzinger reaction performed with 5-bromoisatin yielded 6-*bromo*-2-p-n-*butoxyphenyl*-3-*methylcinchoninic acid*, forming from toluene yellowish microcrystals, m. p. 299—300° (Found: N, 3·2. $C_{21}H_{20}O_3NBr$ requires N, 3·4%), which could be decarboxylated by heat to 6-*bromo*-2-p-n-*butoxyphenyl*-3-*methylquinoline*, shiny colourless leaflets, m. p. 133° (from ethanol) (Found: C, 64·6; H, 5·2. $C_{20}H_{20}ONBr$ requires C, 64·9; H, 5·4%), the picrate of which formed from ethanol silky yellow needles, m. p. 194°.

Oxidation of 1 : 1-*Di*-p-n-*butoxyphenylpropene*.—This ethylene (7 g.), treated with chromic acid (3 g.) in acetic acid, gave 4 : 4′-*di*-n-*butoxybenzophenone*, crystallising as large shiny colourless leaflets, m. p. 121° (Found: C, 77·0; H, 8·0. $C_{21}H_{26}O_3$ requires C, 77·3; H, 8·0%).

4 : 4′-*Diphenoxybenzophenone*. 1 : 1-Di-*p*-phenoxyphenylpropene was obtained from diphenyl ether (60 g.), propionyl chloride (30 g.), and aluminium chloride (45 g.) in benzene, as a thick yellow oil (25 g.), b. p. *ca.* 328—330°/19 mm.; it (7·5 g.) was characterised by oxidation with chromic acid (3 g.) to the *benzophenone*, crystallising from benzene as silky colourless needles, m. p. 139° (Found: C, 81·7; H, 5·2. $C_{25}H_{18}O_3$ requires C, 81·9; H, 4·9%).

Diacylations of Xanthen.—The xanthen was prepared from xanthone by the modified Wolff–Kishner method (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **67**, 2487). A solution of xanthen (18 g.) and acetyl chloride (8 g.) in carbon disulphide (20 c.c.) was treated with aluminium chloride (14 g.), and the mixture worked up in the usual way. After distillation *in vacuo*, the portion, b. p. >250°/15 mm. (3 g.), yielded on recrystallisation 3 : 7-*diacetylxanthen* as shiny, colourless leaflets, m. p. 168°, giving a yellow colour with sulphuric acid (Found: C, 77·0; H, 5·4. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%). 3 : 7-*Dipropionylxanthen* prepared similarly, formed long, silky, colourless needles, m. p. 155° (Found: C, 77·3; H, 6·3. $C_{19}H_{18}O_3$ requires C, 77·5; H, 6·1%). Both ketones gave positive Pfitzinger reactions, and formed high-melting disemicarbazones.

4-n-*Butylbenzophenone*.—A solution of *n*-butylbenzene (30 g.; prepared from bromobenzene, *n*-butyl bromide, and sodium) and benzoyl chloride (40 g.) in carbon disulphide (100 c.c.) was treated with aluminium chloride (40 g.) without cooling, and the mixture kept for 12 hours; the *phenone* (50 g.), a pale yellow fluid oil, had b. p. 214—215°/15 mm., n_D^{20} 1·5729 (Found: C, 85·3; H, 7·4. $C_{17}H_{18}O$ requires C, 85·6; H, 7·6%); the *oxime* formed colourless prisms, m. p. 102° (Found: N, 5·4. $C_{17}H_{19}ON$ requires N, 5·5%). 4-n-*Propylbenzophenone*.

prepared in the same way, was a similar oil, b. p. 200—201°/15 mm., n_D^{22} 1·5831 (Found: C, 85·6; H, 7·2. $C_{16}H_{16}O$ requires C, 85·7; H, 7·1%).

1-p-n-*Butylphenyl*-1 : 2-*diphenylethylene*.—The foregoing butylbenzophenone (24 g.) was added to a cooled Grignard reagent made from benzyl chloride (32 g.) and magnesium (3·5 g.) in ether; the mixture was refluxed for 15 minutes, and worked up in the usual way, the carbinol obtained being dehydrated with 92% formic acid. The *ethylene* formed a pale yellow viscous oil (20 g.), b. p. 262—264°/16 mm., n_D^{20} 1·6264 (Found: C, 92·1; H, 7·7. $C_{24}H_{24}$ requires C, 92·3; H, 7·7%). A cooled solution of this compound (21 g.) in acetic acid (120 c.c.), treated with bromine (10 g. dissolved in acetic acid), yielded 1-*bromo*-2-p-n-*butylphenyl*-1 : 2-*diphenylethylene*, crystallising from acetic acid as colourless leaflets, m. p. 112° (Found: C, 73·5; H, 6·2. $C_{24}H_{23}Br$ requires C, 73·7; H, 5·9%).

1 : 2-*Diphenyl*-1-p-n-*propylphenylethylene*.—Prepared from 4-*n*-propylbenzophenone (34 g.) and benzyl chloride, this *compound* formed a pale yellow viscous oil (32 g.), b. p. 256—257°/16 mm. (Found: C, 92·4; H, 7·6. $C_{23}H_{22}$ requires C, 92·6; H, 7·4%); on treatment in acetic acid solution with bromine (11·3 g.), it (21 g.) yielded 1-*bromo*-1 : 2-*diphenyl*-2-p-n-*propylphenylethylene*, crystallising from acetic acid as shiny colourless leaflets, m. p. 116° (Found: C, 73·1; H, 5·8. $C_{23}H_{21}Br$ requires C, 73·2; H, 5·6%).

TABLE 3.

Ketone	M. p.	B. p./mm.	Formula	Found, %: C	Found, %: H	Reqd., %: C	Reqd., %: H
2-*p*-*n*-Propylbenzoylfuran [a]	*	202°/25	$C_{14}H_{14}O_2$	78·2	6·7	78·5	6·5
4-Ethyl-4′-*n*-propylbenzophenone [a]	*	235/20	$C_{18}H_{20}O$	85·5	8·1	85·7	7·9
4-Methyl-4′-*n*-propylbenzophenone [a]	*	225/20	$C_{17}H_{18}O$	85·5	7·7	85·7	7·6
4 : 4′-Di-*n*-propylbenzophenone [b] ...	*	230/18	$C_{19}H_{22}O$	85·6	8·5	85·7	8·3
2-*p*-*n*-Propylbenzoylthiophen [a]	*	195/20	$C_{14}H_{14}OS$	72·8	6·4	73·0	6·1
4-Chloro-4′-*n*-propylbenzophenone [a]	78°	228/20	$C_{16}H_{15}OCl$	74·1	5·8	74·2	5·8
4-Bromo-4′-*n*-propylbenzophenone [a]	92	233/18	$C_{16}H_{15}OBr$	63·1	5·0	63·4	5·0
4-*p*-*n*-Propylbenzoyldiphenyl [b]	104	270/15	$C_{22}H_{20}O$.	87·8	6·9	88·0	6·7
2-*p*-*n*-Propylbenzoylfluorene [b]	108	*ca.* 280/10	$C_{23}H_{20}O$	88·6	6·3	88·5	6·4
3-*p*-*n*-Propylbenzoylindole [c]	186	—	$C_{18}H_{17}ON$	81·9	6·6	82·1	6·5
2-Methyl-3-*p*-*n*-propylbenzoylindole [c]	172	—	$C_{19}H_{19}ON$	82·0	6	82·3	6·9

* Denotes liquid.

[a] Prepared from *n*-propylbenzene and the corresponding acid chloride. [b] Prepared from *p*-*n*-propylbenzoyl chloride (liquid, b. p. 143°/20 mm.) and the corresponding hydrocarbon. [c] Prepared from *p*-*n*-propylbenzoyl chloride and the corresponding indole by Oddo's method (*Gazzetta*, 1910, **40**, II, 353; 1911, **41**, I, 237; 1913, **43**, II, 210).

1-*Bromo*-2 : 2-*di*-(3-*chloro*-4-*methoxyphenyl*)-1-*phenylethylene*.—To a mixture of *o*-chloroanisole (54 g.), phenylacetyl chloride (24 g.), and phosphorus oxychloride (0·5 c.c.), aluminium chloride (32 g.) was added in small portions; the mixture was kept overnight at room temperature, then heated at 60° on a water-bath for 4 hours. After the usual treatment, 1 : 1-di-(3-chloro-4-methoxyphenyl)-2-phenylethylene (11 g.) was obtained as colourless needles, m. p. 106° (cf. Hoán and Buu-Hoï, *Compt. rend.*, 1947, **224**, 1228). Bromination (0·32 g. of bromine) of this compound (0·75 g.) in acetic acid (10 c.c.) gave 1-*bromo*-2 : 2-*di*-(3-*chloro*-4-*methoxyphenyl*)-1-*phenylethylene* (0·6 g.), crystallising as fine yellowish prisms, m. p. 96° (Found: C, 56·7; H, 3·5. $C_{22}H_{17}O_2BrCl_2$ requires C, 56·9; H, 3·7%).

1-*Bromo*-2 : 2-*di*-(4-*methoxy*-2-*methylphenyl*)-1-*phenylethylene*.—1 : 1-*Di*-(4-*methoxy*-2-*methylphenyl*)-2-*phenylethylene* was obtained from methyl *m*-tolyl ether (65 g.), phenylacetyl chloride (39 g.), and aluminium chloride (50 g.) in the presence of iodine (0·5 g.); it formed from ethanol fine yellowish needles (22 g.), m. p. 78°, b. p. 260°/12 mm. (Found: C, 83·5; H, 7·0. $C_{24}H_{24}O_2$ requires C, 83·7; H, 7·0%); its bromination yielded 1-*bromo*-2 : 2-*di*-(4-*methoxy*-2-*methylphenyl*)-1-*phenylethylene*, crystallising as fine colourless prisms, m. p. 119° (Found: C, 68·0; H, 5·5; Br, 19·6. $C_{24}H_{23}O_2Br$ requires C, 68·1; H, 5·4; Br, 18·9%).

Certain new *ketones* derived from *n*-propylbenzene are recorded in Table 3.

We thank Miss Patricia F. Boshell, M.A. (Oxon.), for assistance.

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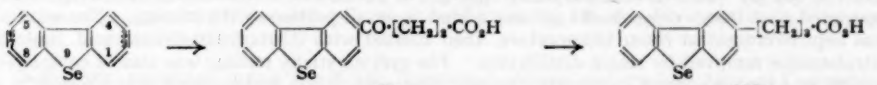
717. *Some Polycyclic Derivatives of Selenophen.*

By Ng. Ph. Buu-Hoï and Ng. Hoán.

Syntheses are described of two isomeric 9-selenanaphthofluorenes, of two dibenzoselenaphenocarbazoles, and of two 9-selenafluorenocarbazoles, and various other selenafluorene derivatives, prepared for biological examination as potential carcinogens. The reactivity of 9-selenafluorene is compared with that of dibenzo-furan and -thiophen.

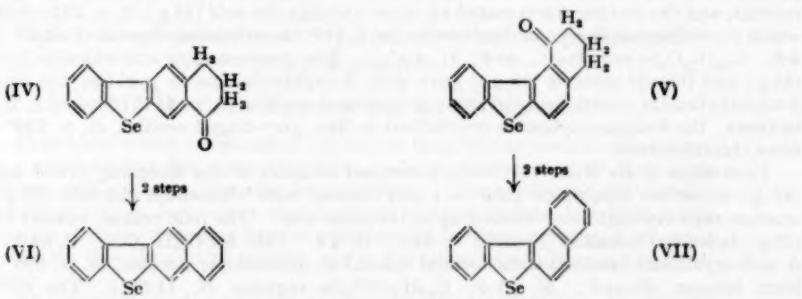
Although several heterocyclic compounds containing oxygen (Barry, Cook, Haslewood, Hewett, Hieger, and Kennaway, *Proc. Roy. Soc.*, 1935, *B*, **117**, 346; Buu-Hoï, *J.*, 1952, 489) and sulphur in a ring (Fieser and Sandin, *J. Amer. Chem. Soc.*, 1940, **62**, 3098; Tilak, 23rd Rep. Brit. Emp. Cancer Campaign, 1946, p. 109; Buu-Hoï and Hoán, *Rec. Trav. chim.*, 1948, **76**, 309; Buu-Hoï, Hoán, Khôi, and Xuong, *J. Org. Chem.*, 1949, **14**, 802; 1950, **15**, 957) have been tested for carcinogenic properties, very little is yet known about similar selenium compounds (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1941, **63**, 2561). Apart from their formal resemblance to carcinogenic hydrocarbons, such molecules would be of biological interest in view of the outstanding toxicity of cyclic selenium compounds already tested (cf. Buu-Hoï, *J.*, 1949, 2882). The present work deals with the preparation, from 9-selenafluorene (I), of several such compounds.

9-Selenafluorene (dibenzoselenophen), discovered by Courtot and Motamedi (*Compt. rend.*, 1934, **199**, 531), is more readily prepared by McCullough, Campbell, and Gould's procedure (*J. Amer. Chem. Soc.*, 1950, **72**, 5753) starting from 2-aminodiphenyl. The



(I) (II) (III)

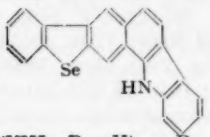
Friedel–Crafts reaction of (I) with succinic anhydride, similarly to that of dibenzothiophen (Gilman and Jacoby, *J. Org. Chem.*, 1938, **3**, 108) gave the keto-acid (II) in excellent yield as sole product, whence Wolff–Kishner reduction readily gave γ-(9-selena-3-fluorenyl)-*n*-butyric acid (III). Cyclisation of the derived acid chloride resulted in a gummy ketonic product, although the equivalent sulphur-compound is known to have a high melting point. The consequent suspicion that a mixture of (IV) and (V) was present was confirmed



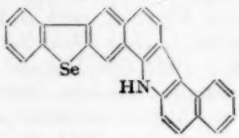
by Wolff–Kishner reduction and subsequent dehydrogenation with selenium to two crystalline 9-selenabenzofluorenes. By analogy, the higher-melting isomer should be 9-selena-2 : 3-benzofluorene (VI), an analogue of brasan (von Kostanekci and Lampe, *Ber.*, 1908, **41**, (2373) and of 2 : 3-benzothiophenanthrene (Mayer, *Annalen*, 1931, **488**, 259; Buu-Hoï and Cagniant, *Ber.*, 1943, **76**, 1269), and the lower-melting one should be the 3 : 4-benzo-compound (VII); similar observations had already been made with dibenzofuran and dibenzothiophen (Gilman and Jacoby, *loc. cit.*). Our inference was rigidly proved by conversion of the higher-melting isomer into 2-phenylnaphthalene by zinc and

Raney alloy powder. The two substances (VI) and (VII) are of interest for cancer research because of their structural relation to 1 : 2-benzanthracene, which is known to produce cirrhosis and hepatomas in rats when administered in the diet (White and Eschenbrenner, *Cancer Res.*, 1945, **5**, 594).

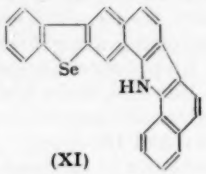
Within the framework of a general investigation into potential carcinogenic carbazoles, we have prepared some polycyclic selenium-containing carbazoles by the usual procedure (cf. Buu-Hoï, Hoán, and Khôi, *J. Org. Chem.*, 1949, **14**, 492), *viz.*, indolisation of the appropriate arylhydrazones of the ketone (IV) and dehydrogenation of the resultant dihydro-compounds by chloranil. Thus were prepared the two hexacyclic compounds (VIII) and (IX), and the two heptacyclic compounds (X) and (XI). In these syntheses,



(VIII; R = H)
(IX; R = Me)



(X)



(XI)

although the oily ketone mixture was used, only one carbazole was obtained in each instance, and the good yields showed that these carbazoles were derivatives of the major constituent (IV) of the ketone mixture.

Experimental

γ-Keto-γ-(9-selena-3-fluorenyl)butyric Acid (II).—To an ice-cooled solution of 9-selenafluorene (54 g.) and succinic anhydride (26 g.) in redistilled nitrobenzene (400 c.c.), finely powdered aluminium chloride (64 g.) was added in small portions with stirring. The mixture was kept overnight at room temperature, then treated with dilute hydrochloric acid, and the nitrobenzene removed by steam-distillation. The greyish sticky residue was almost completely soluble in aqueous sodium carbonate; acidification with dilute hydrochloric acid yielded 72 g. of a solid *acid*, which crystallised as fine colourless needles, m. p. 153°, from benzene, giving an orange colour with sulphuric acid (Found: C, 57·8; H, 3·7. $C_{16}H_{12}O_3Se$ requires C, 58·0; H, 3·6%).

γ-(9-Selena-3-fluorenyl)butyric Acid (III).—A mixture of the foregoing acid (65 g.), 90% hydrazine hydrate (60 g.), potassium hydroxide (70 g.), and diethylene glycol (250 c.c.) was heated with removal of water up to 190—195°, and refluxed for 2 hours. After cooling, the mixture was diluted with water, and acidified with dilute hydrochloric acid. The semi-solid precipitate was taken up in benzene, the solution washed with water, dried (Na_2SO_4), freed from solvent, and the residue fractionated *in vacuo*, yielding the *acid* (52 g.), b. p. 235—240°/0·5 mm., which crystallised as fine, colourless needles, m. p. 119°, from benzene–ligroin (Found: C, 60·4; H, 4·6. $C_{16}H_{14}O_2Se$ requires C, 60·6; H, 4·4%). The corresponding acid chloride [from the acid (45 g.) and thionyl chloride (19 g.)] gave with β-naphthylamine in pyridine the corresponding β-naphthylamide, crystallising in shiny grey-tinged needles, m. p. 217° (decomp.), from chlorobenzene; the 4-diphenylylamide crystallised as fine, grey-tinged needles, m. p. 238° (decomp.), from chlorobenzene.

Cyclisation of the Acid (III).—An ice-cooled solution of the foregoing crude acid chloride (47 g.) in carbon disulphide (250 c.c.) was treated with aluminium chloride (22 g.), and the mixture kept overnight and worked up in the usual way. The pale yellow, viscous oily product (38 g.) failed to crystallise (Found: C, 64·1; H, 4·1. Calc. for $C_{16}H_{12}OSe$: C, 64·2; H, 4·0%). A well crystalline *semicarbazone* formed colourless microscopic needles, m. p. 285° (decomp.), from toluene (Found: N, 11·5. $C_{17}H_{15}ON_3Se$ requires N, 11·8%). The corresponding compound in the dibenzothiophen series had m. p. 280—282° (Mayer, *loc. cit.*). Crystallised chalkone-type compounds were also obtained by condensation with various aromatic aldehydes in the presence of potassium hydroxide; the *p*-chlorobenzylidene derivative formed pale yellow needles, m. p. 220°, from ethanol, giving a brown-red colour with sulphuric acid; the 2 : 4- and 3 : 4-dichlorobenzylidene derivatives showed similar properties; with the piperonylidene compound, the colour with sulphuric acid was deep violet.

The 9-Selenabenzofluorenes (VI) *and* (VII).—The ketonic mixture (10 g.), 90% hydrazine hydrate (25 g.), and potassium hydroxide (25 g.) in diethylene glycol (100 c.c.) were heated with removal of water to 195—200°, and refluxed for 2 hours. After the solution had cooled,

water was added, and the mixture of (IV) and (V) thus obtained was taken up in benzene and yielded, by vacuum-distillation, a viscous, pale yellow oil (95%), b. p. 202—203°/0·6 mm., which partly solidified (Found: C, 67·1; H, 5·1. Calc. for $C_{16}H_{14}Se$: C, 67·4; H, 4·9%). Total separation of the two isomers was not attempted, and this material (6 g.) was heated with selenium powder (3 g.) at 350° for 3 hours. After cooling, the solid mass obtained was taken up in ether, and purified by vacuum-distillation (b. p. 228—230°/0·6 mm.). Fractional crystallisation from ethanol gave the less soluble 9-*selena*-2 : 3-*benzofluorene* (VI) as large, shiny, colourless, sublimable leaflets (3 g.), m. p. 191° (the corresponding sulphur-compound had m. p. 163°) (Found: C, 68·0; H, 3·5. $C_{16}H_{10}Se$ requires C, 68·3; H, 3·6%), and 9-*selena*-3 : 4-*benzofluorene* (VII) (0·8 g.) as large, shiny, colourless leaflets, m. p. 95° (Found: C, 68·4; H, 3·6%); the corresponding picrates formed needles, m. p. 159° (from ethanol) and m. p. 137° respectively. Distillation of (VI) (1 part) with a mixture of zinc and Raney alloy powder (5 parts) yielded 2-phenylnaphthalene, m. p. 101° alone or mixed with a sample prepared otherwise.

Carbazole Syntheses.—In this and the following carbazole syntheses, no attempt was made to isolate the small amounts of the theoretically expected isomeric carbazole. The carbazoles were obtained by heating the crude arylhydrazones with a saturated solution of hydrogen chloride in acetic acid and working up the product in the usual way. 9′-*Selenafluoreno*(2′ : 3′-1 : 2)*carbazole* (VIII) formed fine sublimable, colourless needles, m. p. 336°, from benzene, giving with sulphuric acid a brown colour which rapidly became green (Found: C, 71·6; H, 3·5. $C_{22}H_{13}NSe$ requires C, 71·3; H, 3·5%). Its 6-*methyl* derivative (IX), obtained by *p*-tolylhydrazine, etc., formed fine, sublimable, colourless needles, m. p. >340°, from benzene (Found: C, 72·2; H, 4·0. $C_{23}H_{15}NSe$ requires C, 71·8; H, 3·9%).

9-*Selena*-5′ : 6′-*benzocarbazolo*(1′ : 2′-2 : 3)*fluorene* (X), prepared from β-naphthylhydrazine, formed yellowish, sublimable needles, m. p. >340°, from benzene, giving a violet-brown colour with sulphuric acid (Found: C, 74·5; H, 3·6. $C_{26}H_{15}NSe$ requires C, 74·3; H, 3·5%). Its 7′ : 8′-*benzo*-analogue (XI) formed fine, grey-tinged needles, decomp. >300°, from benzene (Found: C, 74·6; H, 3·5%).

This work, presented before the XIIth Internat. Congress of Pure and Applied Chemistry, New York, September, 1951, was carried out under a grant from the United States Public Health Service (Federal Security Agency), for which the authors express gratitude. Thanks are also offered to Miss Patricia F. Boshell, M.A., for help in this work, and to Messrs. L. Light & Co. for supplies of 2-aminodiphenyl.

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718. *The Spontaneous Optical Resolution of Solvated Tri-o-thymotide.*

By A. C. D. Newman and H. M. Powell.

Crystal-structure examination has shown that tri-*o*-thymotide crystallises as a racemate but that resolution takes place on formation of its crystalline adduct with *n*-hexane, benzene, or chloroform. The crystals do not develop enantiomorphous forms that would permit of hand sorting, but large single crystals of the benzene and hexane compounds have been grown. Each gives a solution showing optical activity which diminishes rapidly through racemisation.

The optical activity arises from hindrance to free rotation about single bonds in a twelve-membered ring. The energy of activation for the racemisation is estimated as 16 kcal./mole.

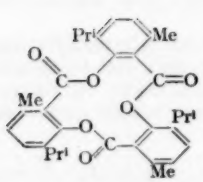
The two thymotides derived from thymotic acid (2-hydroxy-6-methyl-3-*iso*propylbenzoic acid) which were described by Spallino and Provenzal (*Gazzetta*, 1909, **39**, II, 325) as isomeric dithymotides have been further examined by Baker, Gilbert, and Ollis (*J.*, 1952, 1443) and one of these has been found to be tri-*o*-thymotide (I).

If the interatomic distances and bond angles are as shown and rotation about single

bonds is used to minimise steric interference between the carbonyl groups and the substituents on the benzene rings the atoms are not all coplanar. They may be arranged as in Fig. 1. In this the molecule has no symmetry other than a three-fold axis and is therefore not superposable on its mirror image. It could exist in enantiomorphous forms which are related to each other as right- and left-handed three-bladed propellers. One enantiomorph may be converted into the other by rotations about single bonds but in the process some steric interference must be overcome.

Edgerly and Sutton (*J.*, 1951, 1069) have examined the stereochemistry of the same central ring system found in the related tricresotides and trisalicylide. From measurements of dipole moments and other considerations they conclude that these molecules also are propeller-shaped.

There does not seem to be a simple way of effecting a resolution by combining tri-*o*-thymotide with an optically active substance, but during *X*-ray crystallographic examination it became apparent that this compound which crystallises from methanol as a racemate



(I)

FIG. 1. *Scale drawing of a possible form of the trithymotide molecule.*

O=CH$_3$ O=C or CH ◎=Oxygen

C–C (*aromatic*) = 1·4, *other* C–C = 1·54, C=O = 1·25, C–O = 1·43 Å. *Bond angles* 120°, *except those of the isopropyl group and* C–O–C *which are taken as tetrahedral. The thicker end of a tapered line denotes the end nearer to the observer.*

could be resolved by formation of its molecular compounds. This optical resolution has been carried out.

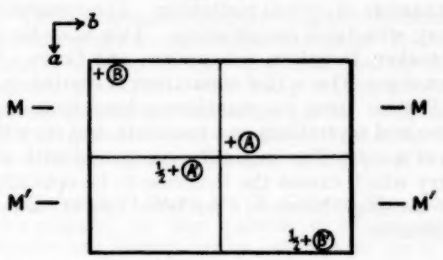
Tri-*o*-thymotide, crystallised from methanol, has an orthorhombic structure. The absent *X*-ray reflexions are those of the space groups C_{2v}^9-*Pbn* or D_{2h}^{16}-*Pbnm*. Of these *Pbnm* may be rejected since with only four molecules in the cell they are required to have either planes or centres of symmetry which are lacking. In the space group *Pbn* the four molecules per unit cell need not have any symmetry and are not restricted to special positions. The structure may be represented as in Fig. 2. Molecule *A* (or *A'*) is derived from *B* (or *B'*) by a reflexion in the plane *MM* (or *M'M'*) perpendicular to the paper, accompanied by a translation of $b/2$. *A* and *B* must be mirror images of each other and hence if tri-*o*-thymotide is a dissymmetric substance the crystals are those of a racemic form containing equal numbers of *dextro*- and *lævo*-molecules.

Baker, Gilbert, and Ollis who found (*loc. cit.*) that a number of substances such as *n*-hexane or benzene unite with tri-*o*-thymotide to give crystalline adducts of the clathrate type provided a crystalline specimen of composition $2C_{33}H_{36}O_6,C_6H_{14}$. It was found to have a hexagonal unit cell containing six molecules of tri-*o*-thymotide and three of *n*-hexane. Since the lattice is not rhombohedral the absent spectra $000l$ when $l \neq 3n$ must be due to a

screw axis of symmetry (3_1, 3_2, 6_2, or 6_4) and the structure belongs to one of the enantiomorphous space groups. The observed equality of ***hkil*** and ***hki$\bar{l}$*** reflexions and the inequality of ***hki*0** and ***khi*0** limit the space group to the enantiomorphous pair $C6_2$, $C6_4$. In these space groups molecules such as tri-*o*-thymotide lacking a two-fold symmetry axis cannot occupy the special equivalent positions of three-fold multiplicity and therefore the six molecules of the unit cell can only be in the general positions. They are all related to each other by rotation and translation operations only and must be geometrically identical. This does not prove that the molecules are dissymmetric but, if they are, then those in any one unit cell are all of the same kind and hence in the absence of complications such as disorders or twinning the molecules in any one crystal are of the same kind, all *dextro* or

FIG. 3. *Face development shown by large crystals of trithymotide–benzene solvate. It is consistent with the symmetry class* 32 *but does not include faces which could distinguish right and left enantiomorphs.*

FIG. 2.



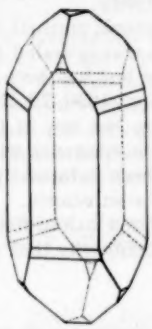
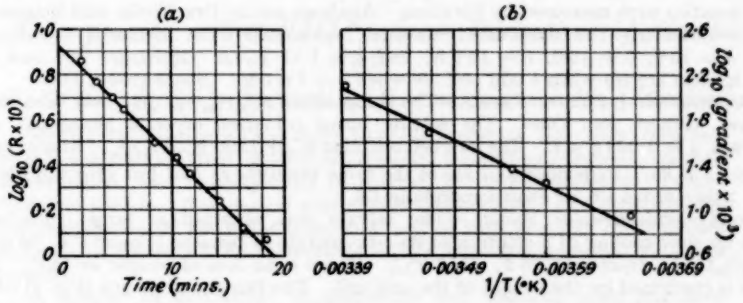


FIG. 4.



all *lævo*. In such a case the separation of the two enantiomorphous forms of the crystals is also a separation of the two molecular antimers.

Crystals of the *n*-hexane adduct were examined under the microscope and on the optical goniometer but were without trace of enantiomorphous faces. They were also cut, and examined in the direction of the optic axis for signs of rotatory power, but in view of the comparatively small dimensions (1 mm.) and their imperfections the negative result is not of great significance. It was planned therefore to make the optical resolution by growing large single crystals which, in the continued absence of enantiomorphous faces but with greater thickness, could be cut and separated according to the sense of the optical rotation observed in the crystal. Alternatively a single large crystal might contain enough material to give a solution showing rotation. The crystals usually grow in needles elongated parallel to the optic axis. They are frequently of a turbid appearance and are difficult material for optical sorting. However the adducts of tri-*o*-thymotide with benzene or chloroform

also give crystals belonging to enantiomorphous space groups. In this case *X*-ray reflexions considered in conjunction with the crystal habit indicate the space groups $C3_121$, $C3_221$. The only special positions require a two-fold symmetry axis in the molecule and are therefore not occupied by tri-*o*-thymotide. Hence the six molecules per unit cell are in general six-fold positions and must be identical, all *dextro* or all *lævo* for any one crystal. No enantiomorphous faces have been observed but crystals of the benzene adduct may be readily grown to the desired size. By slow cooling single crystals up to 1 g. in weight have been obtained.

Solutions in chloroform made in each case from a single crystal rotated the plane of polarisation of light, some to the left and some to the right. The rotation diminished rapidly through racemisation in solution. The rate of racemisation has been determined at temperatures between 0° and 21° and the activation energy estimated. For convenience the main observations have been made on the benzene compound but crystals of the *n*-hexane compound have been obtained large enough (0·019 g.) to give solutions of measurable optical activity.

There are several unusual features of this example of optical resolution. The *possibility* of achieving it was revealed through an *X*-ray structural examination. This is so far a rare occurrence but has been noted by Shoemaker, Donohue, Schomaker, and Corey (*J. Amer. Chem. Soc.*, **1950**, **72**, 2328) for DL-threonine. The actual separation is carried out by hand sorting but not in the manner of Pasteur since no enantiomorphous faces are developed. The substance which has been resolved crystallises as a racemate, but its self-resolution has been induced by the formation of a crystalline molecular compound with an optically *inactive* substance. The dissymmetry which causes the molecule to be optically active arises from a lack of free rotation about the single bonds of a puckered ring of twelve atoms with substituents that cause steric hindrance.

Experimental

X-Ray examinations were made with copper K_α-radiation on oscillating single crystals with stationary or moving films (Weissenberg method). Lattice dimensions are to an accuracy of ½%. Densities were measured by flotation. Analyses are by Drs. Weiler and Strauss, Oxford.

Tri-o-thymotide.—The unsolvated material crystallised from methanol is orthorhombic, having $a = 13{\cdot}5$, $b = 16{\cdot}0$, $c = 13{\cdot}9$ Å, and $\rho = 1{\cdot}17$ g./c.c. Molecules per unit cell = 4. Absent spectra are $0kl$ when k odd and $h0l$ when $h + l$ is odd. Space group, Pbn.

Tri-o-thymotide–n-Hexane Solvate.—The composition $2C_{33}H_{36}O_6.C_6H_{14}$ has been established by Baker, Gilbert, and Ollis. The solvate forms colourless crystals, hexagonal, $a = 14{\cdot}2$, $c = 28{\cdot}9$ Å, $\rho = 1{\cdot}069$ g./c.c. The unit cell contains $3C_6H_{14}$ and $6C_{33}H_{36}O_6$. Absent spectra are $000l$ when $l \neq 3n$. Reflexions $hkil$ are of the same intensity as $hki\bar{l}$ but $hki0$ and $khi0$ are not equal. Space group $C6_3$ or enantiomorphous $C6_4$.

Tri-o-thymotide–Benzene Solvate.—The solvate was obtained in large colourless single crystals by slow cooling of a solution of tri-*o*-thymotide in benzene (Found: C, 76·5; H, 7·0. $2C_{33}H_{36}O_6.C_6H_6$ requires C, 76·2; H, 6·9%). There is no loss of weight at 160°. The composition is confirmed by the weight of the unit cell. The face development (Fig. 3) of pinacoid $\{0001\}$, prisms $\{10\bar{1}0\}$, the large rhombohedron $\{10\bar{1}2\}$, and two small rhombohedra $\{10\bar{1}1\}$ and $\{01\bar{1}2\}$ is consistent with the symmetry class **32** but no enantiomorphous faces were observed. Double refraction is weak, positive. The unit cell has $a = 13{\cdot}7$, $c = 29{\cdot}9$ Å, and contains $3C_6H_6$ and $6C_{33}H_{36}O_6$; $\rho = 1{\cdot}158$ g./c.c. Absent spectra are $000l$ when $l \neq 3n$. Reflexions $hkil$ are not equal to $hki\bar{l}$ but $hki0$ and $khi0$ are equal in intensity. These observations and the crystal habit are consistent with the pair of enantiomorphous space groups $C3_121$, $C3_221$.

Single crystals of about 0·1 g. were powdered and dissolved in 9 c.c. of chloroform, and the resulting solution was examined in a Hilger-Watts Standard polarimeter, Mark III. Some solutions rotated the plane of polarisation to the left, others to the right. The rotation falls to zero owing to racemisation. Table 1 gives rotation against time for a typical experiment. Fig. 4*a* shows a plot of logarithms of rotation against time and from it the value R_0 of the initial rotation is deduced by extrapolation to the estimated zero of time. The straight-line form indicates a reaction of the first order. Table 2 records R_0, calculated for 0·1 g. of material, specific rotations and half-life of the rotation for several temperatures. Five samples were taken from the same crystal; the sixth, from another crystal, gave a specific rotation approximately

the same in magnitude but of opposite sense. Specific rotations are calculated as those of the tri-*o*-thymotide complex. If the rotation is regarded as that of the tri-*o*-thymotide alone the numbers should be multiplied by the factor 1·075. In Fig. 4*b* the logarithms of the gradients of five curves similar to those in 4*a* are plotted against $1/T$; from this the energy of activation for the racemisation is calculated to be 16 kcal./mole.

TABLE 1.—*Racemisation at* 15·2°. *Tri-o-thymotide* (0·1058 *g.*), *in* 9 *c.c. of chloroform, examined in a* 1-*dm. tube.*

Time, mins....	1·8	3·3	4·5	5·8	8·5	10·2	11·8	14·1	16·1	18·3	21·9	24·5
α	0·73°	0·59°	0·51°	0·44°	0·31°	0·27°	0·235°	0·155°	0·135°	0·12°	0·07°	0·045°

TABLE 2.

Temp. (κ)	274·6°	280·2°	283·3°	288·2°	294·6°	294·4°
R_0, calc. for 0·1 g.	0·726°	0·753°	0·743°	0·804°	0·920°	−0·855°
[α]D	+65°	+68°	+67°	+72°	+83°	−77°
Half-life (mins.)	34	17·1	12·4	6·4	2·4	—

Tri-o-thymotide–Chloroform Solvate.—Obtained by cooling or evaporation of solutions of tri-*o*-thymotide in chloroform, this *solvate* (Found : C, 68·9; H, 6·1; Cl, 9·0; $2C_{33}H_{36}O_6,CHCl_3$ requires C, 68·4; H, 6·2; Cl, 9·05%) does not lose weight at 160°. It forms colourless crystals, trigonal, $a = 13{\cdot}55$, $c = 30{\cdot}3$ Å, $\rho = 1{\cdot}209$ g./c.c. The unit cell contains $3CHCl_3$ and $6C_{33}H_{36}O_6$. Absent spectra are $000l$ when $l \neq 3n$. Reflexions *hkil* in general are not equal to $hki\bar{l}$, but *hki*0 is equal to *khi*0 in intensity. The *X*-ray diffraction patterns are very similar to those of the benzene adduct. The space group is not certain but it must be enantiomorphous.

The authors thank Mr. B. Gilbert, Organic Chemistry Department, University of Bristol, who prepared the large quantity of tri-*o*-thymotide used, and Dr. P. W. Kent, Biochemistry Department, Oxford, for his help and the use of the polarimeter.

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719. *Triterpenoids. Part VIII.* Some Derivatives of Siaresinolic Acid.*

By D. H. R. BARTON, N. J. HOLNESS, K. H. OVERTON, and W. J. ROSENFELDER.

Methyl 12 : 19-diketo-18(α)-olean-10-enolate acetate has been prepared by stepwise reaction from siaresinolic acid and by zinc dust reduction, alkaline isomerisation, and re-acetylation of methyl 12 : 19-diketo-olea-10 : 13(18)-dienolate acetate. The partial synthesis from siaresinolic acid substantiates the formulation of the latter compound and in turn provides confirmatory evidence in favour of the correctness of the currently accepted β-amyrin formula.

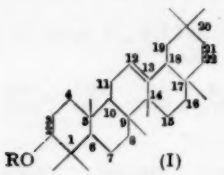
A number of derivatives of siaresinolic and oleanolic acids has been prepared.

The course of selenium dioxide oxidations in the β-amyrin series is discussed and the formation of the end products rationalised.

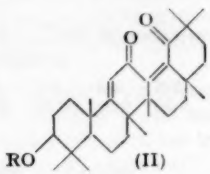
THE formula (I; R = H) for β-amyrin was first proposed by R. D. Haworth (*Ann. Reports*, 1937, **34**, 327). In the great majority of respects this formula is an eminently suitable vehicle for expressing the complex chemistry of the members of the β-amyrin group of triterpenoids. It has received strong support from the formulation of β-amyradienedionol (Jacobs's " keto-diol "; Jacobs and Fleck, *J. Biol. Chem.*, 1930, **88**, 137) as (II; R = H) by Ruzicka and Jeger (*Helv. Chim. Acta*, 1941, **24**, 1236). However, Budziarek, Johnston, Manson, and Spring (*J.*, 1951, 3019) have recently discussed some aspects of β-amyrin chemistry from which, by analogy with a parallel interpretation of common reactions in the α-amyrin series, they conclude that formula (I; R = H) may not be satisfactory in every

* Part VII, *J.*, 1952, 2339.

detail. It appeared to us that the reservations expressed by Spring and his colleagues might be well-founded and that any additional evidence in favour of (I; R = H) for β-amyrin would be welcome. We turned our attention to a substantiation of the expression (II; R = H) for the key compound β-amyradienedionol.



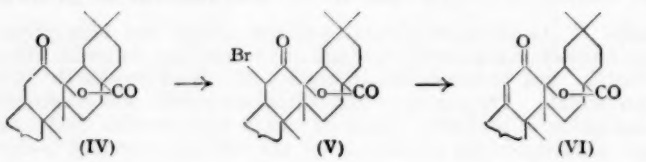
(I)



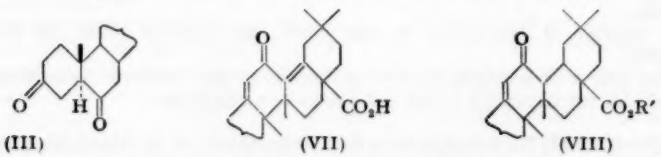
(II)

The formula advanced by Ruzicka and Jeger (*loc. cit.*) for this compound was an adequate representation for the elegant reactions which they reported. In particular it explained the formation of the cyclic pyridazine derivative on heating with hydrazine. However it appeared to us to be a curious feature of the chemistry of β-amyradienedionol that the diene-dione chromophore had never been built up by a stepwise series of reactions and that, in particular, the ketonic oxygen atoms had always been introduced simultaneously. Furthermore the formation of hydrazine derivatives as evidence for a *cisoid*-dione system as in (II; R = H) must be viewed with some reserve for it has been reported that cholestane-3 : 6-dione (III), where a comparable structural feature is absent, forms a monomolecular pyridazine derivative (Seeley and Noller, *J. Amer. Chem. Soc.*, 1948, **70**, 4260, and references there cited).

Our first attempts to build up the diene-dione chromophore by stepwise methods were based on 12-keto-oleananolic lactone acetate (IV; R = Ac). Treatment with bromine in acetic acid gave the corresponding 11-bromo-12-keto-lactone (V; R = Ac). It was hoped that refluxing this with collidine would cause loss of hydrogen bromide to give the lactone (VI; R = Ac), which might be convertible into (VII; R = Ac) : in fact it caused both removal of hydrogen bromide and *reductive* opening of the lactone ring, to give 12-keto-olean-10-anolic acid acetate (VIII; R′ = H), characterised as the methyl ester (Picard, Sharples, and Spring, *J.*, 1939, 1045; Ruzicka, Jeger, and Winter, *Helv. Chim. Acta*, 1943, **26**, 265). Reduction of the 11-bromo-grouping also occurred, as some 12-keto-oleananolic lactone acetate could be recovered.



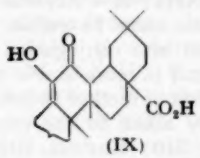
(IV) (V) (VI)

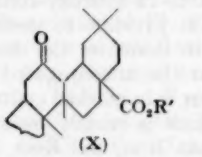


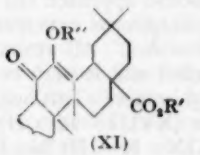
(III) (VII) (VIII)

Oxidation of 12-keto-oleananolic lactone acetate (IV; R = Ac) with selenium dioxide gave a diosphenol-carboxylic acid, characterised as the methyl ester. The acid was at first formulated as (IX; R = Ac) but the methyl ester was also formed by selenium dioxide oxidation of methyl 12-keto-oleananolate acetate (X; R = Ac, R′ = Me). Ruzicka and Jeger (*Helv. Chim. Acta*, 1941, **24**, 1178) have provided compelling evidence that similar oxidation of the analogous 12-keto-β-amyranyl acetate gives a diosphenol system as in (XI). We therefore formulate the selenium dioxide oxidation product of (IV; R = Ac) as (XI; R = Ac, R′ = R″ = H). The presence of the diosphenol grouping was proved by the strong ferric chloride reaction and especially by the characteristic shift in absorption

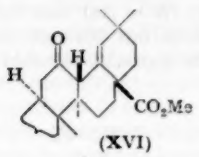
maximum when the acetate methyl ester (XI; R = Ac, R′ = Me, R″ = H) was converted by acetylation into the diacetate methyl ester (XI; R = R″ = Ac, R′ = Me).

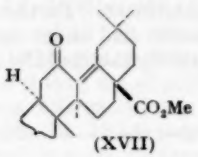

(IX)

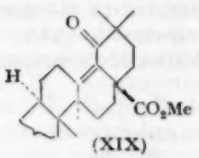

(X)

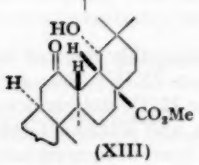

(XI)

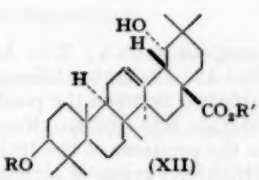
Since these attempts to build up the required chromophore from the 12-keto-lactone seemed unpromising, attention was directed to the use of siaresinolic acid (XII; R = R′ = H) as starting material. Barton, Brooks, and Holness (*J.*, 1951, 278) have shown that the acetate methyl ester (XII; R = Ac, R′ = Me) is readily transformed into methyl 19-hydroxy-12-keto-oleananolate 2-acetate (XIII; R = Ac). Chromic acid oxidation of the latter afforded the corresponding diketone (XIV; R = Ac), which was hydrolysed and isomerised at $C_{(18)}$ by alkali to give methyl 12 : 19-diketo-18(α)-oleananolate (XV; R = H), converted by reacetylation into (XV; R = Ac).* The stereoisomeric acetates (XIV and XV; R = Ac) seemed well suited to the construction of the diene-dione system for both

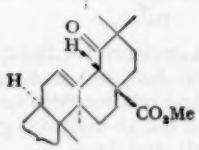

(XVI)

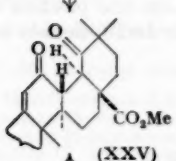

(XVII)

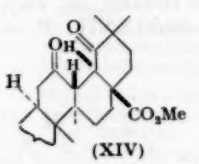

(XIX)

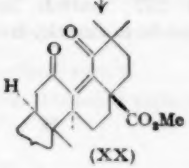

(XIII)

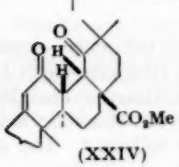

(XII)

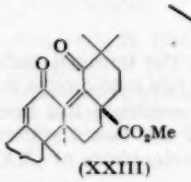

(XVIII)

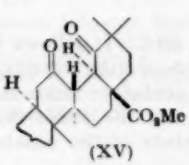

(XXV)


(XIV)


(XX)


(XXIV)


(XXIII)


(XV)

contained ketonic functions at $C_{(12)}$ and $C_{(19)}$. However this did not prove to be the case.

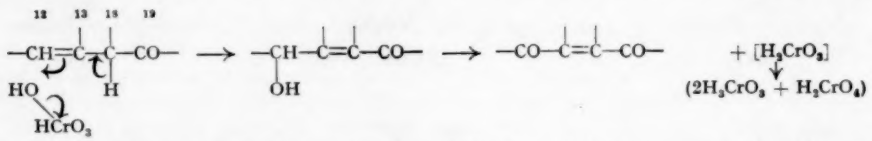
Selenium dioxide oxidation of (XIV; R = Ac) furnished the "O_7"-acetate (Mower, Green, and Spring, *J.*, 1944, 256; cf. Jeger, Norymberski, and Ruzicka, *Helv. Chim. Acta*,

* For stereochemistry see Barton and Holness, *J.*, 1952, 78. The symbols (α) and (β) are employed in the way suggested by Halsall, Jones, and Meakins, *J.*, 1952, 2862.

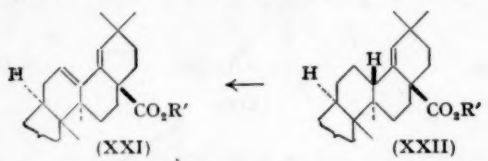
1944, **27**, 1532), which is still of unknown constitution. The isomeric diketone (XV; R = Ac) proved to be inert to selenium dioxide.

In a second approach the 12-keto-19-hydroxy-compound (XIII; R = Ac) was dehydrated by phosphorus oxychloride in pyridine to methyl 12-keto-olean-18-enolate acetate (XVI; R = Ac). All attempts to isomerise the double bond into conjugation to give (XVII) failed and it may be that the unconjugated compound is more stable than the conjugated isomer. This behaviour is in marked contrast to that of methyl 19-keto-olean-12-enolate (XVIII; R = H), which is readily isomerised by alkali to the conjugated isomer (XIX; R = H) (see Bilham, Kon, and Ross, *J.*, 1942, 540; Ruzicka, Grob, Egli, and Jeger, *Helv. Chim. Acta*, 1943, **26**, 1218).

A third approach consisted in preparation of the hitherto unknown methyl 12 : 19-diketo-olean-13(18)-enolate acetate (XX; R = Ac). It was found that this compound was formed, along with (XVIII; R = Ac) and a small amount of the " O_7 "-acetate, by the controlled chromic acid oxidation of methyl siaresinolate acetate. It appears that (XX; R = Ac) results from the oxidation of (XVIII; R = Ac) at $C_{(12)}$ with simultaneous " migration " of the double bond into conjugation with the $C_{(19)}$-keto-group (cf. Fieser and Fieser, " Natural Products Related to Phenanthrene," Reinhold Publ. Corp., 1949, p. 227 *et seq.*). Thus (XX; R = Ac) was obtained by the chromic acid oxidation of (XVIII; R = Ac), whilst the conjugated ester (XIX; R = Ac) was recovered unchanged after being subjected to the same oxidation conditions. Furthermore (XVIII; R = Ac) was not isomerised to (XIX; R = Ac) in acetic acid under the same conditions but without the addition of chromic acid. Mechanistically this could be explained by the formal treatment :



As evidence for the constitution assigned to (XX; R = Ac), it was smoothly reduced by zinc dust and acetic acid to methyl 12 : 19-diketo-oleananolate acetate (XIV; R = Ac). Rigid relationships have been established between the positions of the 12(13)-double bond and the 19-hydroxyl group of siaresinolic acid (Bilham, Kon, and Ross, and Ruzicka, Grob, Egli, and Jeger, *locc. cit.*), between the positions of the 18(19)-double bond of morolic acid (XXI; R = R′ = H) and the 19-hydroxyl group of siaresinolic acid (Barton and Brooks, *J.*, 1951, 257; Barton, Brooks, and Holness, *loc. cit.*), and between the position of the diene system in *iso*dehydro-oleanolic acid (XXII; R′ = H) and the 18(19)-double bond of



morolic acid. It follows then that the terminal carbon atoms of the above-mentioned diene system must correspond to the two keto-groups in methyl 12 : 19-diketo-olean-13(18)-enolate acetate. Since compelling evidence has been advanced (Barton and Brooks, *loc. cit.*) for the *cisoid*-character of the dienic system in *iso*dehydro-oleanolic acid the *cisoid*-nature of the unsaturated chromophore of (XX; R = Ac) follows.* The spatial

* The absorption spectrum of methyl 12 : 19-diketo-olean-13(18)-enolate acetate ($\lambda_{max.}$ 253 mμ, ε = 7000) shows the low intensity of absorption (cf. Barton and Brooks, *loc. cit.*; Turner and Voitle, *J. Amer. Chem. Soc.*, 1951, **73**, 1403; Braude, Bruun, Weedon, and Woods, *J.*, 1952, 1419) to be expected of a *cisoid*-chromophore. Previously Ruzicka and Jeger (*Helv. Chim. Acta*, 1941, **24**, 1236) had tentatively suggested that the hydrogenation product of 12 : 19-diketo-olea-10 : 13(18)-dienyl acetate should be formulated as 12 : 19-diketo-olean-13(18)-enyl acetate. Since the reported absorption was $\lambda_{max.}$ 240 mμ (ε = 10,000) it appears to us that this constitution is not acceptable. In agreement with mechanistic considerations we prefer to regard the hydrogenation product as 12 : 19-diketo-olean-10-enyl acetate.

relationship of the two keto-groups of (XIV; R = Ac) is thus substantiated. Attempts to convert (XX; R = Ac) into the corresponding diene-dione by oxidation with selenium dioxide or with bromine failed.

A correlation between the diene-dione, methyl 12 : 19-diketo-olea-10 : 13(18)-dienolate acetate (XXIII; R = Ac) and siaresinolic acid was finally achieved in the following way. Reduction of (XXIII; R = Ac) by zinc dust and acetic acid gave smoothly methyl 12 : 19-diketo-olean-10-enolate acetate (XXIV; R = Ac). On alkaline hydrolysis followed by reacetylation this was converted into the 18-*iso*-compound, methyl 12 : 19-diketo-18(α)-olean-10-enolate acetate (XXV; R = Ac). The latter was also obtained from (XIII; R = Ac) by bromination, oxidation to the 19-keto-derivative, and dehydrobromination by boiling acetic acid. The presence of the hydrogen bromide produced in the reaction, dissolved in the acetic acid, doubtless accounted for the inversion at $C_{(18)}$. The desired (XXV; R = Ac), although the major product of this reaction sequence, was only isolated with difficulty since it formed stable mixed crystals with a minor proportion of what appeared to be methyl 12 : 19-diketo-olea-10 : 13(18)-dienolate acetate (XXIII; R = Ac). The evidence for this, and the technique adopted for the resolution of the mixed crystals are described in the Experimental section.

It is appropriate at this juncture to consider briefly the course of selenium dioxide oxidation in the β-amyrin series. The more important experimental facts are summarised in the Table. It is clear that the 12 : 19-diketo-10 : 13(18)-diene system is formed from all the possible [10 : 12-, 11 : 13(18)-, and 12 : 18-]dienes, all the monoenes so far studied, and from the only possible (10 : 12 : 18(19)-]triene system, yet it is never produced if oxygen substituents are already present, even if they are at positions 12 and/or 19. An attractive hypothesis to explain this outstanding differentiation is that all the reactions leading to the diketo-diene system proceed *via* the 10 : 12 : 18(19)-triene. Since the triene system has not been reported as an oxidation product in such reactions it is required that it should react more rapidly with selenium dioxide than any of the less unsaturated systems. This has been substantiated in qualitative experiments.

Compound	Selenium dioxide oxidation product	Ref.
β-Amyrin acetate (olean-12-enyl acetate)	12 : 19-Diketo-olea-10 : 13(18)-dienyl acetate; formed *via* olea-11 : 13(18)-dienyl acetate	1
Olean-10-enyl acetate	12 : 19-Diketo-olea-10 : 13(18)-dienyl acetate	2
Olean-13(18)-enyl acetate (δ-amyrin acetate)	12 : 19-Diketo-olea-10 : 13(18)-dienyl acetate	3
Methyl olean-18-enolate acetate (methyl morolate acetate)	Methyl 12 : 19-Diketo-olea-10 : 13(18)-dienolate acetate; formed *via* methyl olea-12 : 18-dienolate acetate	4
Olea-10 : 12-dienyl acetate	12 : 19-Diketo-olea-10 : 13(18)-dienyl acetate and 11-keto-olean-12-enyl acetate	5
Olea-10 : 12 : 18-trienyl acetate	12 : 19-Diketo-olea-10 : 13(18)-dienyl acetate	6
Methyl 12-keto-oleananolate acetate	Methyl 11-keto-12-hydroxy-olean-12-enolate acetate	7
12-Keto-olean-10-enyl acetate	"*iso*-Dienone"	8
11-Keto-olean-12-enyl acetate	"O_5"-acetate	9
11-Keto-olea-12 : 18-dienyl acetate	"O_6"-acetate	10
Methyl 12 : 19-diketo-oleananolate acetate	"O_7"-acetate	7

1, Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1236. 2, Budziarek, Johnston, Manson, and Spring, *J.*, 1951, 3019. 3, Ruzicka, Jeger, and Norymberski, *Helv. Chim. Acta*, 1942, **25**, 457. 4, Experimental, this paper; also Barton and Brooks, *J.*, 1951, 257. 5, Picard and Spring, *J.*, 1941, 35. 6, Newbold and Spring, *J.*, 1944, 532; Norymberski, Thesis, E.T.H., 1946, p. 51. 7, Experimental, this paper. 8, Green, Mower, Picard, and Spring, *J.*, 1944, 527. 9, Mower, Green, and Spring, *J.*, 1944, 256. 10, Jeger, Norymberski, and Ruzicka, *Helv. Chim. Acta*, 1944, **27**, 1532.

Experimental

M. p.s are uncorrected. Rotations were determined in chloroform solution. Values of $[\alpha]_D$ have been approximated to the nearest degree. Ultra-violet absorption spectra were measured for absolute ethanol solutions with the Unicam S.P. 500 Spectrophotometer.

Savory and Moore's standardised alumina for chromatography was used unless specified to the contrary. Light petroleum refers to that fraction of b. p. 40—60°.

The phrase "in the usual way" implies, in general, dilution with water, extraction with

ether, washing successively with aqueous potassium hydroxide (or other more suitable basic reagent), aqueous hydrochloric acid, and water, followed by evaporation of the ethereal solution *in vacuo*. Where necessary, water was removed from the residue by azeotropic distillation with benzene *in vacuo*.

Alkaline hydrolyses were effected by using several equivalents of potassium hydroxide and refluxing the reactants for 30—60 minutes in methanol or dioxan–methanol according to the solubility of the ester.

For methylations with diazomethane the acid was treated with an excess of ethereal diazomethane. After the mixture had been kept at room temperature until the evolution of nitrogen had ceased, the excess of diazomethane and the ether were removed *in vacuo* or on the steam-bath.

Bromination and Dehydrobromination of 12-*Keto-oleanolic Lactone Acetate*.—The keto-lactone acetate (4·97 g.) in " AnalaR " acetic acid (300 ml.) was treated with stirring at 40° with a 50% solution (45 drops) of hydrogen bromide in acetic acid and then with bromine in acetic acid (50 ml. of 1% v/v) at such a rate that the bromine was decolourised as soon as it was added. After 3 hours at 40° and 14 hours at room temperature the colourless plates which had separated were collected. Recrystallisation from chloroform–methanol afforded 11-*bromo*-12-*keto-oleanolic lactone acetate* (2·22 g.), chars at 250°, melts at 314—316° (decomp.), $[\alpha]_D$ ±0° (*c*, 3·20 or 2·96) (Found : C, 64·95; H, 7·9; Br, 13·3. $C_{32}H_{47}O_5Br$ requires C, 64·9; H, 8·1; Br, 13·5%). Dilution of the filtrate and recrystallisation of the precipitate gave a further 1·97 g. of the bromo-ketone.

The bromo-ketone (1·97 g.) was refluxed in redistilled collidine (20 ml.) in a stream of oxygen-free nitrogen for 0·5 hour. Working up in the usual way gave acidic and neutral fractions. Chromatography of the latter over alumina (elution with 1 : 1 to 1 : 4 benzene–light petroleum) gave 12-keto-oleanolic lactone acetate. Recrystallised from chloroform–methanol this had m. p. 277—279°, undepressed on admixture with authentic ketone of the same m. p.; tetranitromethane and Beilstein tests were negative. The acid fraction, after methylation and chromatography over alumina (elution with benzene and 5 : 1 to 4 : 1 benzene–ether) gave methyl 12-keto-olean-10-enolate acetate (1·02 g.). Recrystallised from methanol–light petroleum this had m. p. 203—204°, $[\alpha]_D$ +56° (*c*, 2·81), and gave no depression in m. p. on admixture with an authentic specimen (see Barton and Holness, *J.*, 1952, 78) of the same m. p. Alkaline hydrolysis afforded methyl 12-keto-olean-10-enolate. Recrystallised from methanol with a trace of chloroform this formed long needles, m. p. 231—232°, undepressed in m. p. on admixture with an authentic specimen (McKean, Manson, and Spring, *J.*, 1952, 432) of the same m. p.

Action of Selenium Dioxide on 12-*Keto-oleanolic Lactone Acetate*.—The keto-lactone (500 mg.) in " AnalaR " acetic acid (100 ml.) was refluxed with selenium dioxide (450 mg.) for 4 hours. After being worked up in the usual way the product was separated into acid (365 mg.) and neutral (130 mg.) fractions. On recrystallisation from chloroform–methanol the acidic fraction furnished 11-*keto*-12-*hydroxyolean*-12-*enolic acid acetate* as plates, m. p. 294—296° (decomp.), $[\alpha]_D$ +123° (*c*, 3·13), $\lambda_{max.}$ 289 mμ (ε = 9000), giving a strong green colour with alcoholic ferric chloride (Found : C, 72·65; H, 8·75. $C_{32}H_{48}O_6$ requires C, 72·7; H, 9·15%). Methylation with diazomethane afforded *methyl* 11-*keto*-12-*hydroxyolean*-12-*enolate acetate*. Recrystallised from chloroform–methanol in long needles, this had m. p. 217—218°, $[\alpha]_D$ +109° (*c*, 2·47), $\lambda_{max.}$ 289 mμ (ε = 9000) (Found : C, 73·6; H, 9·35. $C_{33}H_{50}O_6$ requires C, 73·05; H, 9·3%). The ester gave the same colour with ferric chloride as did the parent acid.

The above-mentioned methyl ester (400 mg.) was heated on the steam-bath with " AnalaR " pyridine (10 ml.) and acetic anhydride (5 ml.) for 45 minutes. After working up in the usual way and filtration of the product in benzene through a short column of alumina, there was obtained *methyl* 11-*keto*-12-*acetoxyolean*-12-*enolate acetate* (355 mg.). Recrystallised from methanol–light petroleum this had m. p. 210—211°, $[\alpha]_D$ +79° (*c*, 3·04), $\lambda_{max.}$ 255 mμ (ε = 5000) (Found : C, 71·9, H, 8·95. $C_{35}H_{52}O_7$ requires C, 71·85; H, 8·95%). The diacetate gave no colour with alcoholic ferric chloride.

Action of Selenium Dioxide on Methyl 12-*Keto-oleananolate Acetate*.—The keto-acetate (300 mg.) and selenium dioxide (600 mg.) were refluxed in " AnalaR " acetic acid (30 ml.) for 6 hours. Working up in the usual way furnished a neutral (to sodium carbonate) product (285 mg.). Chromatography over alumina and elution with ether afforded methyl 11-keto-12-hydroxyolean-12-enolate acetate, recrystallising from chloroform–methanol with m. p. 214—216°. There was no depression in m. p. on admixture with the same compound described above. Alcoholic ferric chloride gave a strong green colour. Pyridine–acetic anhydride and working up in the usual way furnished the diacetate; after filtration in benzene solution through

alumina and recrystallisation from methanol–light petroleum, this had m. p. 210—211°, $[\alpha]_D$ +74° (*c*, 1·74), undepressed in m. p. on admixture with the diacetate of the same m. p. described above. The diacetate gave no colour with alcoholic ferric chloride.

Methyl 12-Keto-olean-18-enolate Acetate.—Methyl 19-hydroxy-12-keto-oleananolate acetate ($\lambda_{max.}$ 280 mμ; ε = 60) (1·4 g.), prepared according to the method of Barton, Brooks, and Holness (*J.*, 1951, 278), was heated under reflux with pyridine (10 ml.) and freshly distilled phosphorus oxychloride (2 ml.) for 4 hours. After being worked up in the usual way the product was chromatographed over alumina. Elution with 3 : 7-benzene–light petroleum gave *methyl 12-keto-olean-18-enolate acetate* which, recrystallised from aqueous methanol, had m. p. 178—179°, $[\alpha]_D$ +63° (*c*, 1·57) (Found : C, 74·65; H, 9·4. $C_{33}H_{50}O_5$ requires C, 75·25; H, 9·55%). It had no high intensity absorption above 220 mμ.

Hydrolysis with methanolic potassium hydroxide and working up in the usual way afforded *methyl 12-keto-olean-18-enolate*, m. p. 228—230° (from aqueous methanol) $[\alpha]_D$ +74° (*c*, 1·07) (Found : C, 75·7; H, 10·45. $C_{31}H_{48}O_4,0{\cdot}5CH_3{\cdot}OH$ requires C, 75·5; H, 10·6%). It had no high-intensity absorption above 220 mμ.

In an attempt to effect rearrangement of the 18(19)-double bond to the 13(18)-position, the acetate (80 mg.) in dry methanol (16 ml.) was treated with a solution of sodium (800 mg.) in dry methanol (8 ml.). The absorption spectrum of the solution was determined at intervals. There was no indication of the development of high-intensity selective absorption above 220 mμ even after 120 hours at room temperature or 3 hours' refluxing. Working up in the usual way gave methyl 12-keto-olean-18-enolate, m. p. 232—234°, undepressed in m. p. on admixture with authentic material (see above). The absorption spectrum of the recovered ketone was also checked.

Methyl 12 : 19-Diketo-oleananolate Acetate.—Methyl 19-hydroxy-12-keto-oleananolate (1·3 g.) (Barton, Brooks, and Holness, *loc. cit.*) in " AnalaR " acetic acid (50 ml.) was treated with " AnalaR " chromium trioxide (200 mg.) in 90% acetic acid (10 ml.) and left overnight at room temperature. After working up in the usual way, recrystallisation from methanol containing a trace of chloroform furnished *methyl 12 : 19-diketo-oleananolate acetate* (1·15 g.), m. p. 262—264°, $[\alpha]_D$ +66° (*c*, 1·13), $\lambda_{max.}$ 284 mμ (ε = 90) (Found : C, 73·05; H, 9·2. $C_{33}H_{50}O_6$ requires C, 73·05; H, 9·3%).

Selenium Dioxide Oxidation of Methyl 12 : 19-Diketo-oleananolate Acetate.—The diketone (750 mg.) in " AnalaR " acetic acid (30 ml.) was heated under reflux with selenium dioxide (750 mg.) for 18 hours. After being worked up in the usual way the product was chromatographed over alumina. Elution with benzene furnished the " O_7 "-acetate (330 mg.). Recrystallised from methanol as fine needles, this had m. p. 258—259° after sintering at 248—249°, $[\alpha]_D$ +24° (*c*, 2·23), $\lambda_{max.}$ 225 mμ (ε = 3900), $\lambda_{infl.}$ 292 mμ (ε = 380) (Found : C, 71·2; H, 8·05. Calc. for $C_{33}H_{46}O_7$: C, 71·45; H, 8·35%). There was no depression in m. p. on admixture with an authentic specimen of the " O_7 "-acetate of the same m. p. prepared according to the method of Mower, Green, and Spring (*J.*, 1944, 256).

Methyl 12 : 19-Diketo-18(α)-oleananolate Acetate.—The 18(β)-diketone (220 mg.) was heated under reflux with 10% methanolic potassium hydroxide (25 ml.) for 1 hour. After being worked up in the usual way the product was recrystallised from aqueous methanol, to give *methyl 12 : 19-diketo-18(α)-oleananolate*, m. p. 284—285°, $[\alpha]_D$ +11° (*c*, 2·06) (Found : C, 74·2; H, 9·55. $C_{31}H_{48}O_5$ requires C, 74·35; H, 9·65%). Acetylation with pyridine–acetic anhydride on the water-bath for 30 minutes gave the corresponding *acetate*. Recrystallised from aqueous methanol this had m. p. 304—305°, $[\alpha]_D$ +17° (*c*, 2·04), $\lambda_{max.}$ 283—284 mμ (ε = 100) (Found : C, 73·0; H, 9·35. $C_{33}H_{50}O_6$ requires C, 73·05; H, 9·3%). On attempted oxidation with selenium dioxide as for the 18(β)-isomer (see above), the acetate was recovered unchanged (m. p. and mixed m. p., ultra-violet spectrum) in almost quantitative yield.

Chromic Acid Oxidation of Methyl Siaresinolate Acetate.—The acetate methyl ester (6·0 g.) in " AnalaR " acetic acid (250 ml.) was treated at 40° with " AnalaR " chromium trioxide (2·5 g.) in 95% acetic acid (150 ml.), added dropwise with stirring during 8 hours. Next morning the excess of chromium trioxide was destroyed with methanol (50 ml.), and the mixture worked up in the usual way, to give acid (0·53 g.) and neutral (4·6 g.) fractions. Chromatography (17 fractions) of the neutral fraction over alumina gave the following products : Elution with benzene afforded first methyl 19-keto-olean-12-enolate acetate (715 mg.) (recrystallised from chloroform–methanol), m. p. 243—244°, $[\alpha]_D$ +98° (*c*, 2·27), then material which, when rechromatographed over alumina, gave the " O_7 "-acetate (30 mg.), m. p. 256—258°, $\lambda_{max.}$ 225 mμ (ε = 4200), $\lambda_{infl.}$ 288—298 mμ (ε = 250), undepressed in m. p. on admixture with an authentic specimen (see above), and finally *methyl 12 : 19-diketo-olean-13(18)-enolate acetate* (450 mg.).

Recrystallised from methanol the last had m. p. 248—250°, $[\alpha]_D$ −120° (*c*, 1·21), $\lambda_{max.}$ 253 mμ (ε = 7000) (Found : C, 72·9, 73·65; H, 8·65, 8·65. $C_{33}H_{48}O_6$ requires C, 73·3; H, 8·95%).

Methyl 12 : 19-diketo-olean-12(18)-enolate acetate (50 mg.) in " AnalaR " acetic acid (10 ml.) was stirred under reflux with excess of zinc dust for 2 hours. After being worked up in the usual way and recrystallisation from methanol, the product had m. p. 259—261° $[\alpha]_D$ +66° (*c*, 0·68), undepressed in m. p. on admixture with methyl 12 : 19-diketo-oleananolate acetate (see above). For confirmation of the identity, the reduction product was refluxed with 10% methanolic potassium hydroxide (10 ml.) for 1 hour. After working up in the usual way, reacetylation (pyridine–acetic anhydride on the steam-bath for 30 minutes), and filtration in benzene through alumina, recrystallisation from methanol gave methyl 12 : 19-diketo-18(α)-oleananolate acetate, m. p. 302—304°, undepressed in m. p. on admixture with authentic material (see above).

Chromic Acid Oxidation of Methyl 19-*Keto-olean*-12- *and* -13(18)-*enolate Acetates.*—Methyl 19-keto-olean-12-enolate acetate (120 mg.), in " AnalaR " acetic acid (7·0 ml.), was treated at 40° with " AnalaR " chromium trioxide (60 mg.) in 95% acetic acid (5 ml.) dropwise during 8 hours. After being kept overnight the reaction mixture was worked up as above. Chromatography gave unchanged starting material and methyl 12 : 19-diketo-olean-13(18)-enolate acetate, $\lambda_{max.}$ 254 mμ (ε = 7500), the identity of both compounds being confirmed by m. p. and mixed m. p.

Oxidation of methyl 19-keto-olean-13(18)-enolate acetate (100 mg.) under the same conditions revealed very little uptake (<20% of the theoretical) of chromium trioxide during 2 days at 40°. Working up as above gave back starting material (80 mg.) (m. p. and mixed m. p.).

Methyl 19-keto-olean-13(18)-enolate acetate (100 mg.) in " AnalaR " acetic acid (25 ml.) was kept at 40° for 8 hours; working up gave back unchanged starting material (95 mg.) (m. p. and mixed m. p.).

Chromic Acid Oxidation of Siaresinolic Acid.—Siaresinolic acid (2·0 g.) in " AnalaR " acetic acid (300 ml.) was oxidised as for the methyl ester acetate (see above), but with a proportionate amount of chromium trioxide and working up at room temperature. This gave an acid (1·86 g. and a neutral (0·18 g.) fraction. The acid fraction was methylated and chromatographed over alumina. Elution with benzene gave methyl 2 : 19-diketo-olean-12-enate, m. p. 205—208° (from methanol), converted by being heated under reflux for 1 hour with 25% potassium hydroxide solution and then remethylation into methyl 2 : 19-diketo-olean-13(18)-enate, m. p. 190—192° (from methanol), $\lambda_{max.}$ 252 mμ (ε = 8500). Elution with 9 : 1 ether–benzene and recrystallisation from ethyl acetate–light petroleum afforded *methyl* 2 : 12 : 19-*triketo-olean*-13(18)-*enate* (340 mg.), m. p. 226—228°, $[\alpha]_D$ −137° (*c*, 1·00), $\lambda_{max.}$ 251 mμ (ε = 8700) (Found : C, 74·3; H, 8·85. $C_{31}H_{44}O_5$ requires C, 74·95; H, 8·95%).

Methyl 12 : 19-*Diketo-olean*-10-*enolate Acetate.*—Methyl 12 : 19-diketo-olea-10 : 13(18)-dienolate acetate (205 mg.) (Ruzicka, Grob, and van der Sluys-Veer, *Helv. Chim. Acta*, 1939, **22**, 788) in " AnalaR " acetic acid (20 ml.) was stirred under reflux with excess of zinc dust (400 mg.) for 4 hours. After being worked up in the usual way the product was recrystallised from chloroform–methanol, to give *methyl* 12 : 19-*diketo-olean*-10-*enolate acetate*, m. p. 268—270°, $[\alpha]_D$ +128° (*c*, 1·34), $\lambda_{max.}$ 245 mμ (ε = 12,000) (Found : C, 72·85; H, 8·9. $C_{33}H_{48}O_6$ requires C, 73·3; H, 8·95%).

Methyl 12 : 19-*diketo*-18(α)-*olean*-10-*enolate Acetate.*—The 18(β)-diketone (see above) (1·0 g.) was heated under reflux with 10% methanolic potassium hydroxide (200 ml.) for 1 hour. After being worked up in the usual way the product was acetylated (pyridine–acetic anhydride on the steam-bath for 30 minutes) and then chromatographed over alumina. Elution with benzene gave ten small fractions which were not investigated further. Elution with ether–benzene afforded *methyl* 12 : 19-*diketo*-18(α)-*olean*-10-*enolate acetate* (500 mg.). Recrystallised from methanol this had m. p. 319—320°, $[\alpha]_D$ +82—83° (*c*, 2·62—0·54), $\lambda_{max.}$ 242 mμ (ε = 10,800) (Found : C, 73·25; H, 8·85. $C_{33}H_{48}O_6$ requires C, 73·3; H, 8·95%). The 18(α)-diketone was also formed when the 18(β)-diketone (135 mg.) was heated under reflux with selenium dioxide (135 mg.) in " AnalaR " acetic acid (10 ml.) for up to 5 hours. After being worked up in the usual way and filtered in benzene through alumina the 18(α)-diketone was obtained in essentially quantitative yield (m. p. and mixed m. p.).

Methyl 12 : 19-*Diketo*-18(α)-*olean*-10-*enolate Acetate from Methyl* 19-*Hydroxy*-12-*keto-oleananolate Acetate.*—The hydroxy-ketone (1·0 g.) (see above) in " AnalaR " acetic acid (30 ml.) was treated with a 50% solution (5 drops) of hydrogen bromide in acetic acid and then with 1% (v/v) bromine in acetic acid (9·51 ml., 1 mol.) added during 1·5 hours at 40°. After being kept at room temperature overnight and worked up in the usual way this gave only a neutral product (1·0 g.). A satisfactory crystalline compound could not be isolated at this stage. The crude

reaction product in " AnalaR " acetic acid (100 ml.) was treated with chromium trioxide (125 mg.) in 95% acetic acid (10 ml.) during 1 hour at 40°. A further 50 mg. of chromium trioxide were then added and the solution was kept for a further hour at 40°. After being worked up in the usual way the product, which could not be crystallised, was dissolved in " AnalaR " acetic acid (30 ml.), a 50% solution (4 drops) of hydrogen bromide in acetic acid added, and the solution refluxed for 1 hour. After being worked up in the usual way the neutral product (750 mg.) was chromatographed over alumina. Elution with 4 : 1 benzene–light petroleum and crystallisation from methanol gave in long needles a substance (50 mg.), m. p. 243—244°, $[\alpha]_D$ +58° (*c*, 2·87), +55° (*c*, 1·13), $\lambda_{max.}$ 319 mμ (ε = 15,000) (Found: C, 75·9; H, 9·1%) which was free from bromine. It was not investigated further. Elution with 10 : 1 to 2 : 3 ether–benzene gave seven fractions with m. p.s ranging from 246—249° to 311—314°. These were combined and rechromatographed. Elution with 10 : 1 ether–benzene afforded mixed crystals of methyl 12 : 19-diketo-olean-13(18)-en- and -10 : 13(18)-dien-olate acetates which, recrystallised from methanol, had m. p. 307—309°, $[\alpha]_D$ +34° (*c*, 1·85), +37° (*c*, 1·52), $\lambda_{max.}$ 242 mμ (ε = 9400), $\lambda_{infl.}$ 280 mμ (ε = 2700). A mixture of these two compounds, prepared in such a ratio as to have the same specific rotation, had m. p. 309—310° and an identical ultra-violet absorption spectrum, and was undepressed in m. p. on admixture with above the mixed crystals. Both mixtures gave no depression in m. p. on admixture with methyl 12 : 19-diketo-olean-10-enolate acetate. Repeated crystallisation failed to resolve either the artificial mixture, or that obtained by partial synthesis. Further chromatography was only partly successful.

The mixed crystals (380 mg.) in " AnalaR " acetic acid (30 ml.) were stirred under reflux with zinc dust (500 mg.) for 1·5 hours. After being worked up in the usual way the product (350 mg.) was chromatographed over alumina. Elution with benzene gave material which was not investigated further. Elution with 1 : 19 ether–benzene furnished, after crystallisation from methanol, without difficulty, methyl 12 : 19-diketo-18(α)-olean-10-enolate acetate (130 mg.), m. p. 318—320°, $[\alpha]_D$ +80° (*c*, 2·26—2·12), $\lambda_{max.}$ 242 mμ (ε = 10,800) (Found: C, 72·6; 73·2; H, 8·95, 8·6. Calc. for $C_{33}H_{48}O_6$: C, 73·3; H, 8·95%), undepressed in m. p. on admixture with material of the same m. p., rotation, and absorption spectrum prepared (see above) from methyl 12 : 19-diketo-olean-10 : 13(18)-dienolate acetate.

Action of Selenium Dioxide on Methyl Olea-12 : 18-*dienolate Acetate*.—The methyl ester acetate (methyl *iso*dehydro-oleanolate acetate; Barton and Brooks, *J.*, 1951, 257) (100 mg.) in " AnalaR " acetic acid (25 ml.) was heated under reflux with an equal weight of selenium dioxide for 16 hours. Working up in the usual way gave a neutral product which on chromatography over alumina, elution with 1 : 19 to 1 : 4 ether–benzene, and recrystallisation from chloroform–methanol gave methyl 12 : 19-diketo-olea-10 : 13(18)-dienolate acetate (60 mg.), m. p. 247—248°, $\lambda_{max.}$ 277 mμ (ε = 14,000), undepressed in m. p. on admixture with an authentic specimen (Ruzicka, Grob, and van der Sluys-Veer, *loc. cit.*) of the same m. p. and absorption spectrum.

Relative Selenium Dioxide Oxidation Rates.—The compound (20 mg.), mixed with an equal weight of selenium dioxide, was dissolved in " AnalaR " acetic acid (5 ml.) and rapidly brought to reflux (paraffin-bath). The time required for deposition of red selenium was noted. The following relative oxidation rates were observed : β-amyratrienyl benzoate (Newbold and Spring, *J.*, 1944, 532) (<1 min.), methyl olean-12 : 18-dienolate acetate (Barton and Brooks, *loc. cit.*) (5 mins.), methyl oleanolate acetate (10 mins.), morolic acid, olean-13(18)-enolic acid, and methyl olea-11 : 13(18)-dienolate (all 10—30 mins.).

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720. *Observations on the Reduction of Alkaline 3 : 5-Dinitrosalicylate by Certain Carbohydrates.*

By D. J. Bell, D. J. Manners, and Anne Palmer.

Reduction of alkaline solutions of 3 : 5-dinitrosalicylate can be used for determination of certain methylated derivatives of D-fructose which do not appreciably reduce alkaline copper reagents. Various partially methylated hexoses derived from D-glucose and D-fructose display differing reducing powers, calculated on a molar basis, indicating that factors other than the presence of the potential aldehydic or ketonic group are critical. Feeble or complete lack of reduction was observed with a number of fructosans (inulins, levans, and irisins); this supports the view that these polysaccharides are built up by lengthening the fructosidic chain of the non-reducing sucrose molecule. The dinitrosalicylate reagent is not suitable for determination of the molecular size of certain amylolytic degradation products of starch and glycogen.

Meyer, Noelting, and Bernfeld (*Helv. Chim. Acta*, 1948, **31**, 103) obtained good agreement between estimates of the molecular weights of amylose and of lichenin deduced from certain physical measurements and from the reduction by the polysaccharides of 3 : 5-dinitrosalicylic acid (" DNS ") in alkaline solution (Sumner, *J. Biol. Chem.*, 1921, **47**, 5). Meyer *et al.* interpreted their results on the basis of the assumption that the terminal reducing end-groups of their polysaccharides were oxidised by DNS as was the terminal reducing end-group of maltose.

Chanda, Hirst, Jones, and Percival (*J.*, 1950, 1289) and Chanda, Hirst, and Percival (*J.*, 1951, 1240) found substantial agreement between molecular-size determinations on several xylans when comparing the DNS method with physical determinations. On the other hand, Percival and Ross (*J.*, 1951, 156) noted considerable discrepancies between molecular weights of laminarin assessed from the two different approaches. In an exhaustive investigation on starch, Lansky, Kooi, and Schoch (*J. Amer. Chem. Soc.*, 1949, **71**, 4066) compared the results of several reduction methods with those of physical procedures and concluded, with regard to estimations of molecular weights, that (*a*) hypoiodite methods were inaccurate because of " over-consumption," (*b*) alkaline ferricyanide, copper, and DNS reagents were somewhat more selective but were influenced by pH, reaction temperature, reactant concentration, etc., (*c*) of the (*b*) reagents DNS at 65° gave the most reliable and reproducible results while at 100° higher reductions were obtained, and (*d*) in the starch series none of the values obtained by alkaline reduction methods could be translated into terms of molecular weights.

We have made some investigations of the DNS method with three ends in view, namely, (i) the possible determination of certain methylated fructoses which, by reason of their structures, gave little or no reduction of alkaline copper, (ii) the detection of reducing terminal radicals in certain fructosans, and (iii) the possible estimation of molecular sizes of certain dextrins obtained by amylolytic degradation of glycogen.

While the first aspect of this investigation has yielded satisfactory, but somewhat unexpected, results, the experiments on the fructosans and the dextrins have led us to the same conclusion as Lansky *et al.* (*loc. cit.*).

For our experiments we used the modified reagent of Sumner and Sisler (*Arch. Biochem.*, 1944 **4**, 333; cf. Sumner, *J. Biol. Chem.*, 1924–25, **62**, 287; 1925, **65**, 393). In a few experiments we carried out parallel reductions with the original type of DNS reagent used by Meyer *et al.* (*loc. cit.*). These experiments gave results differing only in numerical values. We found that equal amounts of glucose and fructose reduced equal amounts of DNS (cf. Hostettler, Borel, and Deuel, *Helv. Chim. Acta*, 1951, **34**, 2132) but that considerable variations in " molar " reducing power were exerted by a number of methylated sugars examined. For our purposes, however, it was important to learn that various methylated fructoses, especially those substituted in positions 1 and 3, could be

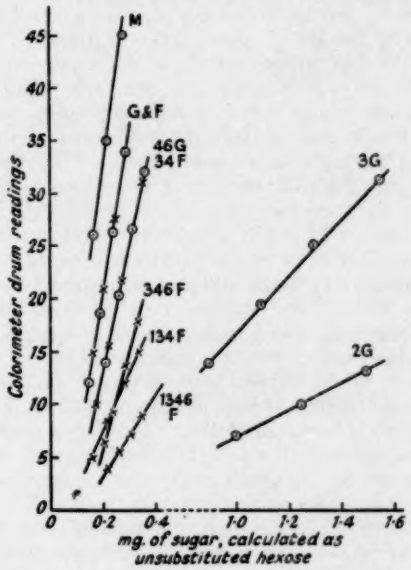
accurately determined on a micro-scale by DNS reduction. Such sugars are not oxidised by alkaline copper and, theoretically at least, are inert towards alkaline hypoiodite. Our results are set forth graphically in the Figure. We shall not comment on the various reducing powers of the sugars examined. It may be noted that the modified DNS reagent markedly decreased the amount of colour produced by *e.g.*, glucose, a fact previously observed by Lansky *et al.* (*loc. cit.*). A further remarkable fact emerged : neither 2 : 3-dimethyl nor 2 : 3 : 6-trimethyl glucoses reduce alkaline DNS, but both 2-methyl and 3-methyl do so, though to a lesser extent than the unsubstituted sugar. Yet the reducing powers of 4 : 6-dimethyl glucose and 3 : 4-dimethyl fructose are closely similar to those of the unsubstituted sugars.

Recent work on fructosans, especially on inulin, has proved that these polysaccharides contain constituent radicals of D-glucose (cf. Palmer, *Biochem. J.*, 1951, **48**, 389; Schlubach and Elsner, *Ber.*, 1929, **62**, 1493). Methylated inulin has been shown by Hirst, McGilvray,

Reducing action of various sugars on alkaline 3 : 5-dinitrosalicylate.

Key :
M = Maltose
G = Glucose
F = Fructose
46G = 4 : 6-Dimethyl glucose
3G = 3-Methyl glucose
2G = 2-Methyl glucose
34F = 3 : 4-Dimethyl fructose
346F = 3 : 4 : 6-Trimethyl fructose
134F = 1 : 3 : 4-Trimethyl fructose
1346F = 1 : 3 : 4 : 6-Tetramethyl fructose

Fructose and derivatives are indicated ×
Glucose and derivatives are indicated ⊙



and Percival (*J.*, 1950, 263) to yield, on hydrolysis, approximately equal amounts of 2 : 3 : 4 : 6-tetramethyl D-glucose and 1 : 3 : 4 : 6-tetramethyl D-fructose, in addition to the major product, 3 : 4 : 6-trimethyl D-fructose. It thus seems highly probable that the inulin molecule is terminated at one end by a *non-reducing* sucrose radical from which the tetramethyl glucose is derived, while the other end consists in a fructofuranoside radical, likewise non-reducing. Strong confirmation of this chemical evidence is afforded by the simultaneous and independent enzymic experiments of Bacon and Edelman at Sheffield (*Biochem. J.*, 1949, **45**, xxvii; 1951, **48**, 114; Edelman and Bacon, *Biochem. J.*, 1950, **47**, 42) and Dedonder at Paris (references to preliminary communications are to be found in the completed papers, *Bull. Soc. Chim. biol.*, 1952, **34**, 144, 157, 171).

Grass levans (Bell and Palmer, *J.*, 1952, 3763; Laidlaw and Reid, *J.*, 1951, 1830), triticin (Arni and Percival, *J.*, 1951, 1822), and irisin (Bell, unpublished), all of which contain component radicals of D-glucose, may also be built up from sucrose acting as a "primer."

If the above hypothesis is true, all these fructosans should contain no reducing terminal radical. As regards inulin, previous reports are conflicting. Irvine and Steel (*J.*, 1920, 1474) found that repeatedly purified inulin was devoid of action on Fehling's solution (cf. Pringsheim and Ohlmeyer, *Ber.*, 1933, **66**, 1292), but Drew and Haworth (*J.*, 1928, 2690)

were unable to purify commercial inulin so that it did not reduce this reagent. Schlubach and Elsner (*loc. cit.*) found several commercial samples which definitely reduced Bertrand's copper reagent, but a sample purified by Kiliani's method (*Annalen*, 1880, **205**, 145) did not. Levan from the grass *Poa trivialis* was noted by Challinor, Haworth, and Hirst (*J.*, 1934, 1560) to be non-reducing (method not stated). Levan from barley leaves (Archbold and Barter, *Biochem. J.*, 1935, **29**, 2689) did not reduce alkaline copper. Triticin (Arni and Percival, *loc. cit.*) reduced Fehling's solution slightly after 15 minutes' heating, but these authors noted a similar reduction with pure sucrose (see below). Schlubach, Knoop, and Liu (*Annalen*, 1933, **504**, 30) found irisin to be non-reducing.

We have found that irisin is completely non-reducing to alkaline copper, but all specimens of inulin, despite repeated crystallisation from water, and all specimens of grass levans, show very slight reduction. It may be that alkaline solutions of heavy-metal ions are not generally suitable reagents for the detection of small proportions of reducing radicals in large molecules (cf. Pringsheim *et al.*, *Ber.*, 1929, **62**, 2378). There are many reports of the apparent "reducing action" of sucrose itself, *e.g.*, by Browne (*J. Amer. Chem. Soc.*, 1906, **28**, 45; *J. Assoc. Off. Agr. Chem.*, 1919, **3**, 261), Maquenne (*Compt. rend.*, 1915, **161**, 617), Quisimbing and Thomas (*J. Amer. Chem. Soc.*, 1921, **43**, 1503), and Bruhns (*Centr. Zuckerind.*, 1929, **37**, 280, 882, 875, 1268, 1467). Moreover several glycosides and other non-reducing polyhydroxy-compounds have been shown to react with alkaline silver (Hough, *Nature*, 1950, **165**, 400). In a personal communication, Dr. H. N. Munro of Glasgow states that many "non-reducing" polyhydroxy-compounds do, in fact, reduce alkaline ferricyanide in presence of nickel ions.

We therefore decided to examine the reducing action of several fructosans on the Sumner–Sisler DNS reagent, choosing this solution as it seemed to be more diagnostic than Sumner's original solution as used by Meyer *et al.* (*loc. cit.*). Samples of irisin from *Iris pseudacorus*, both wild and cultivated, were found to be definitely non-reducing. Samples of levans from Italian rye-grass (*Lolium italicum*) and leafy cocksfoot grass (*Dactylis glomerata*) showed faint reducing properties, unchanged after acetylation and deacetylation; this reduction was only a small fraction of that expected from the molecular weights estimated from sedimentation–diffusion data (Bell and Palmer, *Biochem. J.*, 1949, **45** xiv) or from the glucose radical content (Palmer, *loc. cit.*). Repeatedly recrystallised specimens of inulin behaved similarly. It therefore seems reasonable to suggest that all these fructosans are esentially composed of non-reducing molecules and that any reduction observed is not caused by the presence of reducing terminal radicals.

The DNS reagent was also used in an attempt to determine the reducing power, and hence the degree of polymerisation ("D.P."), of the dextrins "L.D.2" and "L.D.3," produced by the stepwise degradation of rabbit-liver glycogen (Bell and Manners, *Biochem. J.*, 1951, **49**, lxxvii). L.D.2 had a D.P. of 16 when measured by both a hypoiodite method (Kline and Acree, *J. Res. Nat. Bur. Stand.*, 1930, **5**, 1063, modified to a semi-micro-scale by Hanes, personal communication) and an alkaline copper method (Shaffer and Somogyi, *J. Biol. Chem.*, 1933, **100**, 695, as modified by Hanes and Cattle, *Proc. Roy. Soc.*, 1938, *B*, **125**, 387). The reduction of DNS was of an order indicating a D.P. of 5. From its other properties L.D.2 could not possibly be as small as a pentasaccharide. L.D.3 which had a D.P. of 11 (by hypoiodite and alkaline copper methods) behaved as a trisaccharide towards the DNS reagent. Furthermore a sample of a "maltodextrin" (produced by the action of malt α-amylase on starch, and provided by Professor C. S. Hanes, F.R.S.), on examination by the copper method, had a D.P. of 11; the apparent D.P. by the DNS method was 3·7.

Experimental

Standard sugar solutions were made up in saturated benzoic acid and diluted as required. Benzoic acid was found not to interfere with reduction of the DNS reagent.

General Method (Sumner and Sisler, *loc. cit.*).—Suitable amounts of the solution to be examined were measured into glass-stoppered boiling-tubes, and water was added to bring the volume up to 2 ml. The DNS reagent (1 ml., containing 0·63% of 3 : 5-dinitrosalicylic acid) was added to each tube. A blank with water (2 ml.) in place of the carbohydrate solution was prepared similarly. After mixing of the solutions, the tubes were placed in a boiling-water bath,

and heating was continued for 5 minutes. The tubes were then cooled and 5 ml. of water added to each. The intensity of the colour produced was then measured in a photometer, with a green filter, and compared with the colour of the blank. It was noted, with the carbohydrates examined, that prolongation of the heating to 30 minutes did not intensify the colour.

Examination of L.D.2 and L.D.3 and Maltodextrin.—Calibrations of each set of reagents were made at the same time as the measurements on the dextrins—the hypoiodite and copper reagents against standard maltose, and the DNS reagent against glucose and maltose. The Table shows the results.

Reagent	Analysis	L.D.2	L.D.3	"Maltodextrin"
Hypoiodite	Dextrin analysed (mg.)	87·0	77·0	—
	Maltose equiv. (mg.)	11·7	14·8	—
	D.P.	16	11	—
Alkaline Cu	Dextrin analysed (mg.)	16·38	9·96	10·34
	Maltose equiv. (mg.)	2·01	1·79	1·91
	D.P.	16	11	11
D.N.S.	Dextrin analysed (mg.)	1·67	0·58	1·29
	Maltose equiv. (mg.)	0·73	0·24	0·66
	D.P.	4·8	2·8	3·7

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721. *Structural Studies on Inulin from* Inula helenium *and on Levans from* Dactylis glomerata *and* Lolium italicum.

By D. J. Bell and Anne Palmer.

Chromatographic analyses are reported of the hydrolysates of methylated inulin from elecampane (*Inula helenium*) and of methylated levans from two grasses, leafy cocksfoot (*Dactylis glomerata*) and Italian rye (*Lolium italicum*).

The structure of this inulin is similar to that already described for dahlia ("Blue Danube"). Quantitative analyses of grass levan structures are fully reported for the first time.

It has been noted that gravimetric chromatographic analyses may be complicated by the adventitious formation of difructose dianhydrides and similar bodies.

In a previous communication (Bell and Palmer, *J.*, 1949, 2522) we described an effective partition chromatographic method for the quantitative separation of pure tetra-, tri-, and di-methylated fructoses. Separating the hydrolysis products of methylated inulins and grass levans, we encountered an unexpected complication. This difficulty can be circumvented; our experience of such analyses forms the subject of this report.

Analyses of the mixed methylated sugars derived hydrolytically from trimethyl inulin or trimethyl levan requires the separation of relatively small amounts (less than 10%) of 1 : 3 : 4 : 6-tetramethyl D-fructose from the appropriate predominating product, 3 : 4 : 6- or 1 : 3 : 4-trimethyl D-fructose. Again, the latter sugars may have to be separated from small quantities of dimethyl fructoses which have originated either as branch-points or from incomplete methylation. The presence of D-glucose radicals in inulin (cf. Palmer, *Biochem. J.*, 1951, **48**, 389) and in grass levans (Palmer, *loc. cit.*; Laidlaw and Reid, *J.*, 1951, 1830), albeit in small amounts, adds a further analytical problem.

Despite the mild hydrolytic treatment used we find that with methylated inulin, where the predominating radicals are linked 2 : 1′, a non-reducing fructose derivative is present among the hydrolysis products and during the chromatography "loads" the tetramethyl fructose fraction. The latter (Bell and Palmer, *loc. cit.*; Laidlaw and Reid, *loc. cit.*; Arni and Percival *J.*, 1951, 1822) was assayed colorimetrically by strongly acid resorcinol, a

method which does not distinguish between free fructose and such compounds as the non-reducing difructose dianhydrides. This contaminant may well be a hexamethyl difructose dianhydride (see below). However, 1 : 3 : 4 : 6-tetramethyl fructose can be determined, when mixed with non-reducing material, by the reduction of alkaline 3 : 5-dinitrosalicylate (Bell, Manners, and Palmer, *J.*, 1952, **3760**) so that an accurate end-group assay can be made. We obtained an impure specimen of the suspected dianhydride, which can arise in appreciable amounts during hydrolysis of methylated inulin and also possibly when 3 : 4 : 6-trimethyl fructose itself is similarly treated. The material had $[\alpha]_D$ +60° in water, thus resembling 3 : 4 : 6 : 3′ : 4′ : 6′-hexamethyl difructofuranose 2 : 1′-2′ : 1-dianhydride (cf. McDonald, *Adv. Carbohydrate Chem.*, 1946, **2**, 253; McDonald and Turcotte, *J. Res. Nat. Bur. Stand.*, 1947, **38**, 423; Wolfrom, Binkley, Shilling, and Hilton, *J. Amer. Chem. Soc.*, 1951, **73**, 3553).

Methylated grass levans, on the other hand, from their structures might not be expected to yield difructose derivatives of the known 2 : 1′-2′ : 1 types. Nevertheless, in one experiment, we found a tetramethyl fraction contaminated with two additional, essentially non-reducing, ketose derivatives. We therefore emphasise the necessity for rigorous characterisation of chromatographic fractions, especially with ketoses (cf. Bott, Hirst, and Smith, *J.*, 1930, 665; Haworth, Hirst, Jones, and Woodward, *J.*, 1938, 1575). One of us has found evidence (unpublished) that chromatographic fractions of trimethyl fructose can be "loaded" by material arising from 3 : 4-dimethyl fructose. The experience of Bourne, Fantes, and Peat (*J.*, 1949, 1109) with glucose derivatives should also be noted.

The presence of D-glucose derivatives in the hydrolysates of both methylated inulins and levans was confirmed. These appeared mainly as mixtures of all the trimethyl compounds unsubstituted at position 5, the 2 : 4 : 6-isomer predominating, and paper chromatography showed traces of 2 : 3 : 4 : 6-tetramethyl glucose. Although the glucose was not all in the fully methylated form we are prepared to allow that it originated from terminal non-reducing radicals linked as in sucrose (Hirst, McGilvray, and Percival, *J.*, 1950, 1297; Bacon and Edelman, *Biochem. J.*, 1951, **48**, 114; Edelman and Bacon, *Biochem. J.*, 1951, **49**, 446, 529; Dedonder, *Compt. rend.*, 1950, **230**, 549, 994; 1951, **231**, 790, 1134; **232**, 1134, 1442; *Bull. Soc. Chim. biol.*, 1952, **34**, 144, 157, 171; Laidlaw and Reid, *loc. cit.*). The failure of fructosans to reduce, *e.g.*, alkaline 3 : 5-dinitrosalicylate, supports this contention (Bell, Manners, and Palmer, *loc. cit.*).

Inula inulin liberated on hydrolysis 2·9 moles of D-glucose per 100 hexose radicals (conveniently termed 2·9 moles %). If the molecule is terminated by the glucose moiety of a sucrose radical the molecular weight of the polysaccharide would be about 5600 and the chain length 35 radicals. Hydrolysis of the trimethyl inulin gave 1 : 3 : 4 : 6-tetramethyl fructose (1 mol.), 3 : 4 : 6-trimethyl fructose (32·7 mols.), dimethyl fructose (1·5 mols.), and trimethyl glucose (0·54 mol.). Traces of tetramethyl and dimethyl glucoses were observed by paper chromatography. Assuming that the glucose was poorly recovered by the imperfect technique employed (it was roughly equivalent to 50% of glucose in the original inulin) we calculate a chain length of about 36 radicals, corresponding to a molecular weight of 5800. This is the chain-length found for dahlia ("Blue Danube") inulin by Hirst, McGilvray, and Percival (*loc. cit.*) although these authors found chromatographically nearly twice as much glucose in their unmethylated material. Through the friendly co-operation of Professor Hirst and the late Dr. Percival we were able to assay the glucose in two samples, termed "1*a*" and "2*a*" in their paper. Determined by D-glucose oxidase, hydrolysates of these samples contained D-glucose corresponding to 3·0 and 2·0 moles % respectively.

The grass levans, unlike inulin, do not crystallise from water on freezing. They require a relatively high concentration of ethanol (80%) for complete precipitation, and from a comparison of the molecular weights with the methylation data we consider that the "mean" structure consists of a singly branched molecule. The levans as commonly isolated, are clearly not homogeneous; Dr. A. G. Ogston of Oxford University, from sedimentation diffusion data, found for Italian rye-grass levan a molecular weight of about 5500 before dialysis, and 8700 after dialysis for some time. Leafy cocksfoot levan had a molecular weight of the same order (5500). Palmer (*loc. cit.*) found that these two levans, precipitated

in 80% ethanol, contained closely similar amounts of D-glucose radicals (2·7 moles %) corresponding to molecular weights of 6000 and chain lengths (if unbranched) of 37 radicals. She showed, however, that neither was homogeneous since fractions having lower contents of D-glucose radicals were obtained by precipitation at lower alcohol concentrations.

Until recently few quantitative chemical examinations have been made of levans isolated from leaves and stems of grasses by using methylation. Challinor, Haworth, and Hirst (*J.*, 1934, 1560) showed that levan from *Poa trivialis* (rough-stalked meadow grass) yielded crystalline 1 : 3 : 4-trimethyl D-fructose and, assuming that the properties of this material were close to those of bacterial levans on which end-group assays had been done (Challinor, Haworth, and Hirst, *J.*, 1934, 676; Lyne, Peat, and Stacey, *J.*, 1940, 237), suggested a chain-length of about 10—12 fructofuranose radicals. Haworth, Hirst, and Lyne (*Biochem. J.*, 1939, **31**, 786) reported on a specimen of levan isolated from barley leaves by Archbold and Barter (*Biochem. J.*, 1935, **29**, 2689). The latter had noted that the reducing sugar liberated on hydrolysis was not all fructose; this was confirmed by Haworth *et al.* who also showed that the methylated fructosan yielded mostly 1 : 3 : 4-trimethyl D-fructose. Schlubach and Bandmann (*Ann.*, 1939, **540**, 285) attempted the first structural analysis of a graminaceous levan, the so-called " secalin " obtained from the freshly cut stems of rye (*Secale* sp.), obtaining 1 : 3 : 4 : 6-tetramethyl fructose (1 mol.), 1 : 3 : 4-trimethyl fructose (2 mols.), and dimethyl fructose(s) (1 mol.). A similar substance " pyrosin " from freshly cut stems of wheat, examined by Schlubach and Huchting (*Annalen*, 1949, **561**, 173) gave 1 : 3 : 4 : 6-tetramethyl fructose (1·4 mols.), 1 : 3 : 4-trimethyl fructose (3 mols.), and dimethyl fructose (1 mol.). Both polysaccharides showed the presence of small amounts of aldose (unidentified) by the method of Auerbach-Bodländer. Subsequently, a preliminary note on the present work on Italian rye and leafy cocksfoot grasses appeared (Bell and Palmer, *Biochem. J.*, 1949, **45**, XIV), followed by the work of Laidlaw and Reid (*loc. cit.*) on perennial rye grass (*Lolium perenne*).

Leafy cocksfoot levan was examined in two fractions, (*a*) precipitated (100%) in 80% ethanol, and (*b*) precipitated (86%) in 62% ethanol. These fractions are hereafter termed " levan-80 " and " levan-62." The results of methylation experiments, followed by chromatographic analyses of the hydrolysis products are given in Table 1. Trimethyl " levan-80 " was partly (40%) soluble in acetone at room temperature; the soluble and insoluble fractions were examined separately; trimethyl levan-62 was completely insoluble in acetone. No search for glucose derivatives was made during the analyses of levan-80, but levan-62 was investigated as described below. These results demonstrate that this levan is not homogeneous, and also that its structure differs from those of the fructosans examined by Schlubach and his co-workers.

TABLE 1. *Levan from leafy cocksfoot grass.*

	Levan-80		Levan-62
D-Glucose radicals (moles %)	2·9		2·2
Mol. wt., calc. from above	5600		7400
Mol. wt., by ultracentrifuge (Dr. A. G. Ogston)	5500		—
Trimethyl derivatives :			
Yield (%)	75		80
	Acetone-sol. (40%)	Acetone-insol. (60%)	
OMe (%)	42·5	42·5	45·3
D-Fructose derivatives found in hydrolysates :			
1 : 3 : 4 : 6-Me_4 (mols.)	1	1	1 *
1 : 3 : 4-Me_3 (mols.)	11	13	22
? Me_2 (mols.)	2	1·6	0·5
Chain length	14	15—16	23—24
Mol. wt. of chain	2300	2700	3900

* This fraction was initially contaminated. See Experimental section for assay procedure.

The column-chromatogram fractions from levan-62 were examined by paper chromatography for the presence of glucose derivatives. Traces of 2 : 3 : 4 : 6-tetramethyl glucose and a relatively large amount of trimethyl isomers were found, the latter contaminating the dimethyl fructose fraction. This trimethyl glucose was concentrated by appropriate chromatographic treatment, 1·6% of the total sugars present in the hydrolysate

being obtained as a crystalline mixture in which 2 : 4 : 6-trimethyl glucose predominated. Varying smaller amounts of the 2 : 3 : 4-, 2 : 3 : 6-, and 3 : 4 : 6-isomers were also present.

Italian rye grass levan was also examined, but less exhaustively. By methylation through the acetate, an 80% yield of trimethyl levan (OMe, 45·8%) was obtained. Our results are summarised in Table 2.

TABLE 2. *Levan from Italian rye grass.*

D-Glucose radicals (moles %)	Mol. wt., calc. from glucose content	Mol. wt., from ultra-centrifuge (Dr. Ogston)	D-Fructose derivatives found in hydrolysate of trimethyl levan: 1 : 3 : 4 : 6-Me_4 (mols.)	1 : 3 : 4-Me_3 (mols.)	Me_2 (mols.)	Chain length	Mol. wt. of chain
2·8	5800	5500	1	11	1	13	2100

Comparison with the levan from *Lolium perenne* examined by Laidlaw and Reid (*loc. cit.*) is of interest. Here the chain length was 25—30 radicals; 2 moles % of D-glucose radicals were present; and chromatographic examination of a boiled aqueous solution showed the presence of sucrose.

We have carried out control experiments in which chromatographically pure specimens of the appropriate sugars were subjected to the exact hydrolytic treatment and chromatography used in fructosan investigations. With 1 : 3 : 4-trimethyl fructose there was no interference with the quantitative recovery of pure 1 : 3 : 4 : 6-tetramethyl fructose. On the other hand, when 3 : 4 : 6-trimethyl fructose was a component of the mixture there was slight " loading " of the tetramethyl fraction by a non-reducing fructose derivative. This indicates that condensation of free fructose derived radicals may occur in dilute acid solution.

EXPERIMENTAL

Unless otherwise stated, the following standard procedures were employed throughout: (*a*) Solvents were evaporated under reduced pressure below 40°. (*b*) Polarimetric observations were made in aqueous solutions in 2-dm. tubes. (*c*) Paper chromatograms were made with Whatman No. 1 paper and *n*-butanol–water. Ketoses and aldoses were detected by the resorcinol and aniline phthalate sprays respectively. As temperature-controlled tanks were not available, all chromatograms were run in the presence of authentic specimens of the appropriate sugars. (*d*) Column chromatography and the characterisation of methylated fructoses were done according to Bell and Palmer (*loc. cit.*). (*e*) The glucose-radical content of the fructosans was determined by Palmer's method (*loc. cit.*).

Methylations.—The following general procedure was used. One part of polysaccharide was dissolved in 3 parts (v/w) of 30% (w/v) sodium hydroxide solution. With vigorous stirring at 40°, 30 parts (v/w) of methyl sulphate and 60 parts (v/w) of 30% sodium hydroxide solution were added in one-tenth portions at 10-minutes' intervals. Dioxan was added from time to time to promote solution of the methylated product which tended to separate at an early stage. Finally 30—40 parts of hot water were introduced and the whole heated at 100°, with stirring, for an hour. The methylated fructosans separated and were collected by filtration, washed with boiling water, and treated as required.

Hydrolysis of Methylated Fructosans.—One part of polysaccharide was dissolved in 5 parts (v/v) of boiling ethanol, and 7 parts (v/v) of 0·05N-sulphuric acid were added slowly. After 4 hours' heating at 95—100° under reflux the ethanol was removed by distillation at ordinary pressure. After addition of water to replace the ethanol which had distilled, heating was continued until the optical rotation was constant. The solution was brought to pH 7 with barium carbonate and after filtration concentrated to about 50 ml. for examination by paper chromatography (Bell and Palmer, *loc. cit.*).

Quantitative Analysis.—Fructose (ketose) was determined by the method of Cole, Hanes, Jackson, and Loughman (cf. Bell and Palmer, *loc. cit.*). Reducing sugars were determined by reduction of alkaline 3 : 5-dinitrosalicylate (Bell, Manners, and Palmer, *loc. cit.*).

Isolation of the Polysaccharides.—(*a*) *Inulin.* Fresh roots of elecampane harvested in October 1947 were treated according to Onslow (" Plant Biochemistry," 1929, Cambridge Univ. Press, p. 60). The crude inulin, recrystallised three times from water (pH 8—8·5) by freezing the solution to −20° and allowing it to thaw slowly, had $[\alpha]_D$ −41·0° and contained 2·9 moles % of D-glucose radicals.

(*b*) *Levans.* Pure strains of dried grasses were extracted by Bacon's method (Palmer, *loc. cit.*). Levans from leafy cocksfoot and from Italian rye-grass had $[\alpha]_D$ −40·5° and −41·0° respectively.

Methylated Inulin : Chromatographic Analysis.—10 G. of inulin yielded 10 g. (80%) of trimethyl derivative, $[\alpha]_D^{20}$ −52·8° (in chloroform) (Found : OMe, 45·1%). 7·47 G. were hydrolysed and analysed on the partition column, with two extra intermediary elutions; each eluted fraction was examined by paper chromatography (Table 3). Quantitative examinations of each fraction was made by both the ketose and dinitrosalicylate methods. Each fraction was characterised as fully as possible (cf. Bell and Palmer, *loc. cit.*). The results are summarised in Table 4.

TABLE 3. *Analysis of hydrolysate of trimethyl inulin from* Inula helenium.

	Column chromatography :		Paper chromatography :			
			Fructose spots :		Glucose spots :	
Serial no. of fraction	Eluting solvent and no. of column-lengths passed	Wt. of material eluted (g.)	main R_F	trace R_F	main R_F	trace R_F
1	Toluene–0·33% EtOH (16)	0·5	0·78 [a]	—	—	0·79 [b]
2	Chloroform (8)	6·8	0·67 [c]	—	—	?0·76 [b] ?0·64
3	Chloroform–5% Bu^nOH	0·13	—	0·67 [c]	0·60	—
4	Chloroform–10% Bu^nOH	0·12	0·44	0·67 [c]	—	0·60 0·46
5	Methanol	0·20	0·44	—	—	0·37

[a] Same R_F as 1 : 3 : 4 : 6-tetramethyl fructose. [b] Same R_F as 2 : 3 : 4 : 6-tetramethyl glucose.
[c] Same R_F as 3 : 4 : 6-trimethyl fructose.

TABLE 4. *Examination of the fractions from Table* 3.

Serial no. of fraction	Composition of fraction	Analytical constants and remarks
1	0·23 g. of 1 : 3 : 4 : 6-tetramethyl fructose 0·27 g. of non-reducing material, ? hexamethyl difructose dianhydride	Impossible to characterise
2	6·80 g. of 3 : 4 : 6-trimethyl fructose	Virtually pure; $[\alpha]_D^{18}$ +30·3°; n_D^{20} 1·4658; OMe, 41·6%; oxidation by IO_4^- (pH 7·5) gave 1·0 mol. of CH_2O
3	0·01 g. of trimethyl fructose 0·12 g. of trimethyl glucose	Examined separately (see below), $[\alpha]_D$ −70°
4	0·12 g. of dimethyl fructose	Combined fractions, essentially dimethyl fructose; $[\alpha]_D^{18}$ −43·4°; n_D^{20} 1·4852; OMe, 26·9%; oxidation by IO_4^- (pH 7·5) gave 1·5 mols. of CH_2O
5	0·20 g. of dimethyl fructose	

Recovery of sugars was 7·8 g. (96%) present in the following molar proportions : tetramethyl fructose, 1·0; trimethyl fructose, 32·7; trimethyl glucose, 0·54; dimethyl fructose 1·5. Examination of fraction 3 (0·13 g.) showed that it contained 8·2% of trimethyl fructose. The amount of aldose was therefore 0·12 g. From the specific rotation, the $[\alpha]_D$ of the glucose fraction must have been of the order of +74°, typical for a trimethyl D-glucopyranose.

Paper chromatography (ethyl methyl ketone–water and *n*-butanol–water systems) showed 2 : 4 : 6-trimethyl glucose to be the main component, admixed with small amounts of all the other pyranose isomers.

Levan from Leafy Cocksfoot.—For the methylation experiments two distinct preparations were used : (*a*) " levan-80 " obtained by complete precipitation in ethanol at 80% concentration, and (*b*) " levan-62 " where 86% of the levan was precipitated in ethanol at 62% concentration. The glucose-radical contents were 2·9 moles % for " levan-80 " and 2·2% for " levan-62." Both samples were methylated twice. Trimethyl " levan-80 " (75% yield) had OMe, 42·5% (not raised by repeated treatment with Purdie's reagents); " trimethyl levan-62 " (80% yield) had OMe, 45·3%.

Trimethyl " Levan-80."—Only 40% of this methylated levan was soluble in acetone at room temperature, unlike the material from *Poa trivialis* (Challinor, Haworth, and Hirst, *loc. cit.*) Both soluble and insoluble portions had OMe, 42·5%. Analysis of the hydrolysis products from both fractions gave similar results. No search was made for glucose derivatives. Results are in Table 5.

The amounts of fractions marked * were insufficient for accurate determination of $[\alpha]_D$. n_D^{20} and R_F values of the single spots given on paper chromatograms, compared with authentic 1 : 3 : 4 : 6-tetramethyl fructose, indicated that both fractions 1 were composed essentially of the latter sugar.

Fractions 2 and 3, in each case, were homogeneous with respect to fructose derivatives, on paper chromatograms. Fractions 2 were crystalline and were essentially 1 : 3 : 4-trimethyl D-fructose. Fractions 3 must, from their $[\alpha]_D$, have been composed of dimethyl fructoses unsubstituted on position 6.

TABLE 5. *Analysis and characterisation of the hydrolysis products of the acetone-soluble and acetone-insoluble portions of trimethyl "levan-80."*

Fractions were eluted by the following solvents: 1, toluene–0·33% ethanol; 2, chloroform–5% *n*-butanol; 3, methanol.

Acetone-soluble portion (2·87 g. hydrolysed)

No. of fraction	Eluted (g.)	R_F	n_D^{20}	OMe (%)	$[\alpha]_D^{18}$	Molar ratio
1	0·20	0·8	1·4509	*	*	1
2	2·14	0·6	1·4653	40·0	−57·2°	11
3	0·33	0·4	1·4820	28·0	−60·4	2

Recovery: 88% of theoretical fructose content

Acetone-insoluble portion (1·18 g. hydrolysed)

No. of fraction	Eluted (g.)	R_F	n_D^{20}	OMe (%)	$[\alpha]_D^{18}$	Molar ratio
1	0·076	0·8	1·4509	*	*	1
2	0·96	0·6	1·4658	42·0	−56·0°	13
3	0·11	0·4	—	28·8	−60·6	1·6

Recovery: 89% theoretical fructose content

Trimethyl "Levan-62."—This was completely insoluble in acetone at room temperature. After hydrolysis and analysis on a silica column each fraction eluted was examined by paper chromatography. Faint traces of tetramethyl and dimethyl glucose were detected in the appropriate fractions, but the bulk of the glucose appeared as trimethyl derivatives and was concentrated in the dimethyl fructose fraction. The first "ketose" fraction, *i.e.*, that expected to contain 1 : 3 : 4 : 6-tetramethyl fructose as sole component, contained two additional substances strained by the acid resorcinol spray. The amount of tetramethyl fructose in the mixture, determined by dinitrosalicylate, was about one-third of the total material eluted (see Table 6).

TABLE 6. *Hydrolysis products of trimethyl "levan-62."*

11·60 G. of trimethyl levan were hydrolysed. Eluting solvents were as in Table 5.

No. of fraction	Eluted (g.)	R_F: Fructose derivative	R_F: Glucose derivative	OMe (%)	$[\alpha]_D^{18}$	n_D^{20}	
1	0·80	0·75 0·82 [a] 0·89	(Trace 0·81) [b]	52·5	+14·7° [c]	1·4511 [d]	0·54 g. of reducing Me_4 fructose was chief component
2	11·08	0·60	(Traces, 0·81, 0·6)	41·3	−56·1	1·4662	Almost pure crystalline 1 : 3 : 4-Me_3 fructose
3	0·30	(Trace 0·6) 0·4	0·6 (Trace 0·4)	—	—	—	A complex mixture (see below)

[a] R_F of 1 : 3 : 4 : 6-tetramethyl fructose. [b] R_F of 2 : 3 : 4 : 6-tetramethyl glucose. [c] $[\alpha]_D$ of 1 : 3 : 4 : 6-tetramethyl fructose, +30°. [d] n_D^{20} of 1 : 3 : 4 : 6-tetramethyl fructose, 1·4506.

The presumed 3 : 4 : 6 : 3′ : 4′ : 6′-hexamethyl difructose 2 : 1′-2′ : 1-dianhydride found in hydrolysates of inulin has the same R_F value as tetramethyl fructose. The component of R_F 0·75 might be tetramethyl ethylfructoside (*cf.* Haworth and Learner, *J.*, 1928, 619). The component of R_F 0·89 might be 1 : 3 : 4-trimethyl ethylfructoside (cf. Arni, Thesis, Univ. Edinburgh, 1951), or a dimer of that sugar as suspected by Lyne, Peat, and Stacey (*J.*, 1940, 237).

Recovery of sugars was 12·18 g. (95·5%) present in the following molar proportions: tetra-, 1·0, tri- 22·0, and di-methyl fructose, 0·6, corresponding to a chain length of *ca.* 24 radicals.

Fraction 3 (0·3 g.) was partitioned on a silica column through which were passed eight column-lengths of chloroform–10% (v/v) *n*-butanol. The eluate contained 0·1 g. of a syrup, $[\alpha]_D^{18}$ +44°, composed of a relatively high concentration of trimethyl glucoses (paper chromatography). Extraction of the silica by methanol gave 0·2 g. of a syrup, $[\alpha]_D^{18}$ −7·5°, n_D^{20} 1·4838 [OMe, 26·9%; IO_4^- oxidation (pH 7·5) yielded 0·48 mol. of formaldehyde]. This fraction appeared to be a mixture of dimethyl fructoses. Glucose derivatives were absent (paper chromatography).

Investigation of the Glucose-containing Fractions from Trimethyl "Levan-62."—A sample of trimethyl levan was hydrolysed as before and the resulting sugars transferred to a silica column

and fractionally eluted as described for methylated inulin (Table 3). The chromatographic scheme and the results of paper chromatography are shown in Table 7.

TABLE 7. *Qualitative chromatographic examination of the hydrolysate of trimethyl "levan-62."*

	Column chromatography	Paper chromatography			
		Fructose components detected:		Glucose components detected:	
No. of fraction	Eluting solvent and no. of column-lengths passed	Main	Trace	Main	Trace
1	Toluene–0·33% EtOH (16)	Me_4	—	—	Me_4
2	Chloroform (8)	Me_3	—	—	Me_4
3	Chloroform–5% Bu^nOH (8)	—	Me_3 Me_2	Me_3	Me_3
4	Chloroform–10% Bu^nOH (8)	Me_3	Me_3	—	Me_3 Me_2
5	Methanol	Me_3	—	—	Me_3

In this experiment tetramethyl fructose in fraction 1 was unaccompanied by other fructose derivatives. The trimethyl glucose was concentrated in fraction 3.

Fraction 3, which represented 1·6% of the total sugars found in the hydrolysate, rapidly crystallised. The crystal habit differed from that of 1 : 3 : 4-trimethyl fructose, but resembled that of 2 : 4 : 6-trimethyl glucose. Exhaustive comparison, by paper chromatography, made with authentic samples of the 2 : 3 : 6-, the 2 : 3 : 4-, the 2 : 4 : 6-, and the 3 : 4 : 6-isomer showed that fraction 3 consisted mainly of 2 : 4 : 6-trimethyl glucose.

Levan from Italian Rye-grass.—Air-dried levan (10 g.) was methylated through the acetate (cf. Challinor, Haworth, and Hirst, *loc. cit.*). The resulting precipitate, after being washed and dried in a high vacuum, weighed 6·8 g. (80%) (Found: OMe, 45·8%) and had $[\alpha]_D^{18}$ −54·5° in chloroform. No attempts were made to fractionate this levan by means of acetone.

Analysis of the Hydrolysis Products of Trimethyl Levan from Italian Rye-grass.—The levan (0·94 g.) was hydrolysed and the resulting sugars analysed on the partition column. Careful examination of the three methylated fructose fractions failed to reveal contaminants. The eluted fractions were: (1) 1 : 3 : 4 : 6-tetramethyl fructose (0·08 g., 1 mol.), (2) crystalline 1 : 3 : 4-trimethyl fructose (0·77 g., 11 mols.), and (3) dimethyl fructose (0·06 g., 1 mol.). Recovery of fructose components was 89·5%.

Control Experiments.—These were done to determine whether the hydrolytic procedure was responsible for the production of difructose dianhydrides or similar substances from pure samples of the appropriate monosaccharides. Ternary mixtures of previously chromatographed fructose derivatives were boiled with 0·03N-sulphuric acid for 8 hours and then isolated and chromatographed as were the methylated fructosans. In each case 1 : 3 : 4 : 6-tetramethyl and 3 : 4-dimethyl fructose were used, the trimethyl fructose being the 1 : 3 : 4- or the 3 : 4 : 6-derivative. Results are in Table 8.

TABLE 8.

			Recovered weight			
Expt. no.	Fructose component	Starting wt. (g.)	Ketose method	Gravimetric method	Dinitrosalicylate method	Characterisation of recovered sugars
1	1 : 3 : 4 : 6-Tetramethyl	0·70	70	—	70	OMe, 50·0%; $[\alpha]_D$ −28·0° (*c*, 3·0); n_D^{30} 1·4506; R_F 0·8
	1 : 3 : 4-Trimethyl	0·30	—	0·3	—	OMe, 41·0%; $[\alpha]_D$ −56·0 (*c*, 1·5); n_D^{30} (fused) 1·4661; R_F 0·6. IO_4^- gave 1·0 mol. of CH_2O
	3 : 4-Dimethyl	1·15	—	1·10	—	OMe, 29·2%; $[\alpha]_D$ −58° (*c*, 1·0); n_D^{30} 1·4850; R_F 0·4
2	1 : 3 : 4 : 6-Tetramethyl	0·25	0·29	—	0·25	R_F 0·8. Single spot uncontaminated by trimethyl sugars
	3 : 4 : 6-Trimethyl	1·78	—	1·77 *	—	OMe, 41·6%; $[\alpha]_D$ +28·1° (*c*, 3·0); n_D^{30} 1·4648; R_F 0·6. IO_4^- gave 1·0 mol. of CH_2O
	3 : 4-Dimethyl	0·11	—	0·11	—	OMe, 29·6%; $[\alpha]_D$ −61·5° (*c*, 0·6); n_D^{30} 1·4840; R_F 0·4

* Corrected for 0·4 g. of "difructose dianhydride" contaminating the tetramethyl fraction.

Attempts to Separate the Supposed "Hexamethyl Difructose Anhydride" from Tetramethyl Fructose.—A relatively large amount of the contaminated tetramethyl fructose fraction of inulin

hydrolysates was collected. Chromatography on paper did not indicate possibilities of separation in this way. Attempts to distil away the monomeric sugar at room temperature were unsuccessful as the anhydride proved to be equally volatile. Steam-distillation likewise effected no significant separation between the amounts of reducing and non-reducing components. Finally, by distillation in an apparatus of the type described by Ellis (*Chem. and Ind.*, 1934, 77) when the condenser was cooled by water and not by the usual acetone–solid carbon dioxide, a distillate was obtained which contained only 3% of reducing tetramethyl fructose. This material had $[\alpha]_D$ +62·5° (cf. McDonald, *loc. cit.*, who quotes $[\alpha]_D$ +50° for hexamethyl difructose dianhydride-I) (Found: OMe, 46·6. $C_{13}H_{32}O_{10}$ requires OMe, 45·6%).

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722. *The Stability of the Complexes of the Group* IIA *Metal Ions.*

By R. J. P. WILLIAMS.

An account is given of the factors which affect the stability of the complex ions of the alkaline-earth metals. It is shown that a simple theory based on purely electrostatic interactions is not sufficient to explain the data available and that short-range repulsion forces must also be considered. Further, it is suggested that the latter interaction terms account for the low stability of many magnesium complexes. A brief outline of the significance of entropy changes in affecting the stability of complexes is also incorporated. Finally, reference is made to the extension of these ideas to the activity coefficients and the solubilities of the salts of the metals in aqueous solution.

THEORETICAL discussions of the properties of the compounds of the Group IIA metals usually characterise them as arising from the electrostatic interactions between the bivalent cations and oppositely charged ions or orientated dipoles. This treatment is supported by various types of evidence: the close agreement between the experimentally observed lattice energies and those determined by the use of the Born–Haber cycle which assumes (see p. 3772) that only electrostatic forces exist between the interacting ions (Born and Mayer, *Z. Physik*, 1932, **75**, 1); the very small differences between the experimental heats of hydration and those calculated from a simple ionic model (Bernal and Fowler, *J. Chem. Phys.*, 1933, **1**, 515); the low ionisation potentials of the metals which are thought strictly to limit covalency; the activity coefficients of the bivalent ions in halide salt solutions which are those to be expected from the activity laws (Stokes, *Trans. Faraday Soc.*, 1948, **44**, 295); the values of the dissociation constants of some of the complexes of these metals (Jones, Monk, and Davies, *J.*, 1949, 2693); and the practically complete absence of complexes with uncharged ligands such as ammonia (Bjerrum, "Metal Ammine Formation in Aqueous Solution," Hasse and Son, Copenhagen, 1941). Nevertheless, a simple explanation of the chemistry of aqueous solutions of magnesium, calcium, strontium, and barium ions is impossible (cf. Table 1). The stability constants for complexes of these metals are true thermodynamic constants and all the values from different authors are therefore directly comparable. In a second compilation (Cannan and Kibrick, *J. Amer. Chem. Soc.*, 1938, **60**, 2314) the stability constants of the complexes of the alkaline-earth metals are internally consistent but inconsistent with those in Table 1, for they are uncorrected for the ionic strength of the medium in which the measurements were made. However, despite the difference in absolute values, the same relations are apparent between the constants of both sets. For this reason the data have been used later in this paper (Table 3). In Table 1 the constants, log k_M, *i.e.*, the logarithm of the stability constant of a metal with

a given ligand, are taken from the literature and refer to aqueous solution. The stability constant, k_M, for a complex with a unidentate ligand, *e.g.*, the acetate ion or the sulphate ion, has not the same meaning as that for a polydentate ligand, *e.g.*, the oxalato-group, because the latter can co-ordinate through two groups forming a chelate ring. However, this distinction cannot be made satisfactorily, for the number of oxygen atoms through which each co-ordinating group combines is not always known.

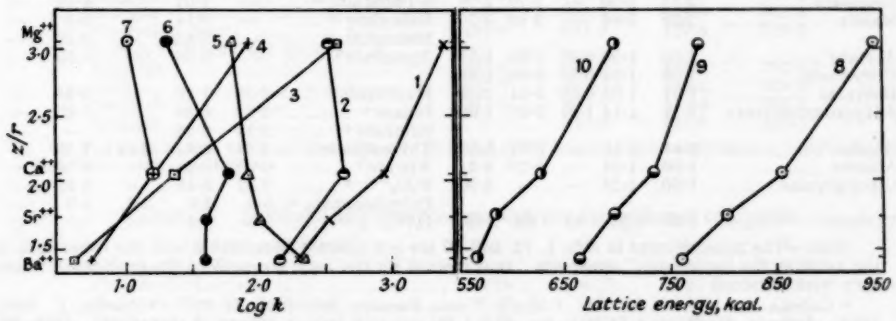
A second difficulty arises because it has become customary to call many of these complexes " ion-pairs " in order to differentiate them from the more covalent complexes. Although the necessity for some such distinction is apparent, it is clear that the process of complex formation can be described in two stages :

$$M(H_2O)_n + L \rightleftharpoons \underset{\text{Ion-pair}}{M(H_2O)_nL} \rightleftharpoons \underset{\text{Complex}}{ML(H_2O)_m} + (n - m)H_2O$$

As it is not possible to say, as yet, to what extent each of these processes occurs in some cases, it has been necessary to discuss the stability constants initially in terms of the overall reaction, as this leads to a simpler examination of the data. It seems likely, however, that in some systems the stability-constant data refer to different stages of the above reaction

FIG. 1. *Plot of the logarithm of the stability constant of some of the complexes (Table 1) against z/r, where z is the charge on the metal ion and r its radius.*

FIG. 2. *Plot of the lattice energies of some of the salts of the alkaline-earth metals against z/r. (cf. Fig. 1).*



1, Oxalate. 2, Malate. 3, Hydroxyl. 4, Alanine. 5, Thiosulphate. 6, Tartrate. 7, Glycylglycine. 8, Oxides. 9, Sulphides. 10, Fluorides.

N.B. The tartrate data are not strictly comparable with the others (see notes to Table 1).

even in the series of the alkaline-earth metals, and that they might easily refer, for example, to the formation of an ion-pair in the case of the magnesium salt and to a complex in that of the barium salt with the same anion. The general argument outlined here is not invalidated by such considerations, as shown later (p. 3775), but the distinction is of importance for the discussion of the activity coefficients and the solubility of the salts of the Group IIA metals as the degree of hydration may vary with the concentration of the solution. If now the basic assumption is made that the complexes are formed as the result of the electrostatic interactions between the cations and the negative charge of the ligands, then the order of stability of the complexes for a given ligand should be in the inverse order of the radii of the cations, *i.e.*, Mg > Ca > Sr > Ba :

	Mg	Ca	Sr	Ba
Ionic radius, Å	0·66	0·99	1·15	1·37

Furthermore, a linear relation between the free-energy change for the formation of the complex, which is proportional to log k_M, and the ionic potential, z/r, where z is the charge on the cation and r its radius, might well have been expected (see Davies, *J.*, 1951, 1256). It is clear from Fig. 1 that no such simple relation exists, and that deviations to low magnesium stabilities often occur. For organic acid complexes the values of log k_M of the magnesium complex are increasingly smaller than those of the calcium complex the greater the number of the groups through which the ligand can co-ordinate. An exception to this

appears in the glycine complexes (Table 1) but in this case the ligand contains a highly polarisable amino-group. In the iodate, thiosulphate, nitrate, and possibly the sulphate complexes the indications are that the stability sequence is completely reversed (Table 1).

A somewhat similar effect can be observed in the lattice energies of the Group IIA metal salts (Table 2) when they are plotted against z/r (Fig. 2). However, in this case although the values for the magnesium salts are low, no change of the expected order occurs. The relatively low values of the lattice energies of the magnesium salts here arise through the increasing repulsion forces between the anions concomitant with the diminishing size of the cation. This is particularly important in the case of magnesium, for the size of its ion is such that the anions come into " contact " with one another before they come into " contact " with the central ion : this has been discussed at length by Pauling (" Nature of the Chemical Bond," pp. 352—372, Cornell Univ. Press, 1941). Likewise, in the calculation of heats of hydration of these cations, Bernal and Fowler (*loc. cit.*) obtained agreement with the experimental data by allowing for similar repulsion terms.

These ideas on the effect of repulsion between non-bonded atoms cannot be extended

TABLE 1. *Stability constants, log* k_M, *of complexes of the alkaline-earth metals.*

Ligand	Mg	Ca	Sr	Ba	Zn	Ligand	Mg	Ca	Sr	Ba	Zn
Oxalate [2]	3·43	3·00	2·54	2·33	4·89	Nitroacetate [9] ...	−0·17	−0·30	—	—	—
Malonate	2·85	2·49	—	1·71	3·68	Citrate [10]	—	3·17	2·92	2·98	—
Succinate	2·15	2·00	—	1·70	2·70	*o*-Phthalate [10] ...	—	1·07	—	0·92	—
Malate	2·52	2·66	—	2·19	3·70	Salicylate [10]	—	0·14	—	0·0	—
						Maleate [11]	—	2·43	—	2·26	—
Acetate	1·05	1·00	0·97	0·93	1·57	Fumarate [11] ...	—	2·00	—	1·59	—
Propionate	1·08	1·04	0·97	0·88	1·55						
Butyrate	1·07	1·05	0·90	0·84	1·54	Hydroxide [3]	2·58	1·40	—	0·64	—
β-Hydroxybutyrate	1·14	1·14	1·01	0·97	1·60	Iodate [4]	0·72	0·89	—	1·05	—
						Sulphate [5]	2·15	2·28	—	—	—
Glycine	3·44	1·43	—	0·77	5·52	Thiosulphate [6]	1·84	1·92	2·04	2·33	—
Alanine	1·96	1·24	—	0·77	5·21	Nitrate [7]	0·00	0·28	—	0·92	—
Glycylglycine	1·06	1·24	—	—	3·80	$P_3O_9^{---}$ [8]	3·32	3·46	—	3·35	—
						Polyphosphate [12]	3·2	3·0	2·8	3·0	—
Tartrate [1]	1·36	1·80	1·65	1·62	2·68	HPO_4^{--} [13]	2·5	2·4	—	—	—

Note.—The measurement in refs. 1, 12, and 10 are not directly comparable with the other data in the table as the former are " constants " uncorrected for the ionic strength of the medium in which they were obtained

[1] Cannan and Kibrick, *loc. cit.* [2] Monk, *Trans. Faraday Soc.*, 1951, **47**, 297. [3] Davies, *J.*, 1951, 1257. [4] Jones, Monk, and Davies, *loc. cit.* [5] Money and Davies, *Trans. Faraday Soc.*, 1932, **28**, 609. [6] Denney and Monk, *ibid.*, 1951, **47**, 789. [7] Righellato and Davies, *ibid.*, 1930, **26**, 390. [8] See ref. 4. [9] Pedersen, *Acta Chem. Scand.*, 1949, **3**, 676. [10] Joseph, *J. Biol. Chem.*, 1946, **164**, 529. [11] Topp and Davies, *J.*, 1940, 87; see also Peacock and James, *J.*, 1951, 2233. [12] Van Vazer and Campanella, *J. Amer. Chem. Soc.*, 1950, **72**, 655. [13] Greenwald, Redish, and Kibrick, *J. Biol. Chem.*, 1940, **135**, 65.

(References in this table are often to papers in which some of the data were originally tabulated; in these papers there are very many detailed references.)

directly to the discussion of the formation of a complex in solution, for in this case the stability of the bond is measured relative to the hydrate stability (Jones, Monk, and Davies, *loc. cit.*). However, the effect of this complication can be seen from the differences, Δ, between the lattice energies of salts with a constant anion and the heats of hydration of the corresponding cations (Table 2). The values of Δ fall in no particular sequence. In the replacement of water by a ligand in a complex, therefore, repulsion terms are likely to destroy the order expected of stabilities as given by the ionic potential.

To return to the data in Table 1 and in Fig. 1, the stability of the hydroxides increases almost linearly with the ionic potential and hence the repulsion terms must be small. The same sequence occurs in the mono- and di-carboxylic acid complexes, but the linear relation is not obeyed presumably owing to the repulsion around the cation between the ligand and an unknown number of water molecules. For the chelated complexes two factors alter as the ring size increases. First, the stability of the ring diminishes—this appears in the fall in the stability constants for all the metal complexes through the series oxalate, malonate, succinate, and glutarate despite the fact that the changes in the acid dissociation constants favour stronger complexes as the ring size is increased. Secondly,

the volume occupied by the liquid around the central ion increases slightly with the size of the ring. It is observed, as expected, that this has the greatest effect in the magnesium complexes, *e.g.*, in the replacement of oxalate by succinate (Table 3). The effect of the introduction of further groups into the ligand is seen in the hydroxy-dicarboxylic acid complexes. In the tartrates the magnesium ion is the least able of all the cations to form a complex. As all the tartrates are more stable than the succinates, despite the lower acidic constants, the hydroxy-groups must play some part in the complexes (Table 3). It is interesting too that the order of the stability of the magnesium complexes follows the order of the acid dissociation constants from malate to tartrate, but the converse is true of the barium and strontium complexes. A similar difference between magnesium and the other three ions appears in the hydroxy-monocarboxylic acid complexes in which there can be no doubt that the hydroxy-groups play some part. The complexes of the larger cations gain most in stability from the substitution of hydroxy-groups in the simple acid anions. These points can be simply interpreted in terms of the suggested " crowding " effect.

TABLE 2.* *Theoretical lattice energies (kcal.) of some salts.*

Salt	Mg	Ca	Sr	Ba
Fluoride	699·2	620·2	581·8	558·9
,, (exptl.)	692·3	621·0	585·2	549·8
Oxide	946·3	846·8	803·0	755·1
Sulphide	781·0	726·4	692·2	660·3
Selenide	—	701·5	671·5	641·3
Hydration (heat)	464·0	381·9	349·8	316·2
Δ (Salt — Hydrate) (see p. 3772)				
Fluoride	235·2	238·3	232·0	232·7
Oxide	482·3	464·9	453·2	438·9
Sulphide	317·0	344·5	342·4	344·1
Selenide	—	319·6	321·8	325·1

* The data in this table are from Paul (" Principles of Chemical Thermodynamics," McGraw-Hill, New York, 1951, p. 158).

TABLE 3. *Differences of complex stability on the exchange of ligands.*

Ligands exchanged	Mg	Ca	Sr	Ba
Acetate/Glycollate	0·41	0·58	0·37	0·27
Propionate/Lactate	0·39	0·57	0·27	0·21
Butyrate/Hydroxybutyrate	0·07	0·09	0·11	0·12
Propionate/Glycerate	0·32	0·68	0·46	0·46
Butyrate/Gluconate	0·17	0·70	0·64	0·64
Malonate/Malate	−0·36	0·34	0·20	0·07
Succinate/Tartrate	0·16	0·60	0·59	0·59
Oxalate/Succinate *	−1·28	−1·00	—	−0·63

Note. The differences of stability, log k_M, listed in this table are those between the metal complexes of the second- and of the the first-named ligand with the same metal ion. (Data from Cannan and Kibrick, *J. Amer. Chem. Soc.*, 1938, **60**, 2314, except that those marked * are from Table 1.)

In Table 1 there are also some stability constants for amino-acid complexes. The crowding effect would seem to be the cause of the low magnesium stability in the glycylglycine complex, compared with its high stability in the glycine and alanine complexes.

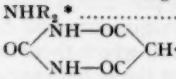
The zinc ion has a radius of 0·72 Å, whence the effect of steric factors on the stability of its complexes should be similar to that for magnesium. This is shown by the data in Table 1—despite the much greater overall stability of the zinc complexes through greater covalency.

In Table 4, another set of data, due to Schwarzenbach *et al.*, is presented. A dominating feature is the reduction of the stability of any chelate complex consequent upon an increase in the ring size. More important for present purposes is the reduction of the stability of the magnesium complexes relatively to those of calcium and the other cations, upon increase in the number of positions through which the ligand can co-ordinate. This factor is sometimes sufficient to reverse the stability order expected from the ionic potentials for magnesium and calcium complexes. The alternations in the relative stability of the complexes of these two metals as a new ligand group is substituted *ortho*, *meta*, and then *para* to the original group in a benzene ring, is very significant of the size of this steric factor.

However, throughout all the series of these ligands there is no change in the order of stabilities Ca>Sr>Ba.

From the above discussion it is possible to understand why the stability of the magnesium complex is sometimes lower than that of the other ions, but no explanation has been given for the stability sequences observed with the anions of the strong inorganic acids,

TABLE 4. *The stability constants, log* k_M, *of some further Group* IIA *metal complexes.*

Ligand	Mg	Ca	Sr	Ba	Ref.
NHR_2 *	3·66	3·41	—	1·67	1
	8·85	8·77	7·6	6·8	2
$Ph{\cdot}NR_2$	1·15	0·6	—	—	3
o-$C_6H_4(SO_3H){\cdot}NR_2$	2·68	4·57	3·50	3·48	
m- ,,	1·26	1·26	—	—	
p- ,,	1·15	0·95	—	—	
o-$C_6H_4(CO_2H){\cdot}NR_2$	3·91	5·06	3·91	3·57	
m- ,,	1·38	1·46	$\leqslant$1·00	<1·00	
p- ,,	1·30	1·30	<1·0	<1·0	
o-$C_6H_{10}(NR_2)_2$ †	10·3	12·5	—	—	4
m- ,,	4·64	4·77	—	—	
p- ,,	4·30	4·19	—	—	
NR_3	5·41	6·41	4·94	4·82	5
$NR_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$	5·28	5·04	3·87	3·40	
$[CH_2]_2(NR_2)_2$	8·69	10·59	8·63	7·76	6, 7
$[CH_2]_3(NR_2)_2$	6·02	7·12	5·18	4·24	
$NR_2{\cdot}CH_2{\cdot}PO_3H$	6·28	7·18	5·59	5·35	5
$NR_2{\cdot}CH_2{\cdot}CH_2{\cdot}PO_3H$	6·33	5·44	4·10	3·64	
$NR_2{\cdot}CH_2{\cdot}CH_2{\cdot}SO_3H$	3·48	4·15	3·26	3·01	
$[CH_2]_4(PO_3H)_2$	2·77	2·54	—	2·28	8

* R = $CH_2{\cdot}CO_2H$. † C_6H_{10} = 1 : 2-*cyclo*Hexylene residue.

[1] Schwarzenbach, Kampitsch, and Steiner, *Helv. Chim. Acta*, 1945, **28**, 1133. [2] *Idem, ibid.*, 1946, **29**, 364. [3] Schwarzenbach, Willi, and Bach, *ibid.*, 1947, **30**, 1303. [4] Schwarzenbach and Ackermann, *ibid.*, 1949, **32**, 1682. [5] Schwarzenbach, Ackermann, and Ruckstuhl, 1949, **32**, 1175. [6] Schwarzenbach and Ackermann, *ibid.*, 1948, **31**, 1029. [7] *Idem, ibid.*, 1947, **30**, 1798. [8] Schwarzenbach, Ruckstuhl, and Zurc, *ibid.*, 1951, **34**, 455.

e.g., with the iodate, nitrate, and thiosulphate ions (Table 1). In this connection it is interesting to examine the free-energy change, ΔG, occurring on the formation of a complex by reaction (1):

$$M(H_2O)_n + L \longrightarrow ML + nH_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

ΔG is the sum of the heat and entropy changes of this reaction, whence

$$\Delta G = -\boldsymbol{R}T \ln k_M = \Delta H - T\Delta S$$

The entropy change will always be such as to favour the formation of the complex as a neutralisation of charge is involved (cf. Frank, *J. Chem. Phys.*, 1945, **13**, 478); *e.g.*, in the formation of the barium thiosulphate complex, $\Delta S = -18{\cdot}8$ cals./°C, $\Delta H = -2{\cdot}6$ kcal. (Davies and Wyatt, *Trans. Faraday Soc.*, 1949, **45**, 770); in the formation of the zinc malonate complex $\Delta S = -27{\cdot}5$ cal./°C, $\Delta H = -3{\cdot}1$ kals. (James, *J.*, 1951, 153). Further examples are provided by the work of Davies on the lanthanum ferricyanide complex (*Proc. Poy. Soc.*, 1948, **195**, *A*, 116) and of Rabinowitch and Stockmayer on the ferric complexes with chloride, bromide, and hydroxyl ions (*J. Amer. Chem. Soc.*, 1942, **64**, 335). The gain in entropy arises from the partial loss of hydration on complex formation, and for a series of alkaline-earth complexes with a given ligand it should be proportional to the entropy of hydration of the cations, *i.e.*, in the order Mg > Ca > Sr > Ba (cf. Rabinowitch and Stockmayer, *loc. cit.*). However, the heat energy changes in these reactions, ΔH, can be either positive or negative as has been shown by measurements on the hydrogen-ion complexes (Latimer, *Chem. Reviews*, 1936, **18**, 349; Pitzer, *J. Amer. Chem. Soc.*, 1937, **59**, 2365) and by the work cited in the above references. Now it is the sum of the heat and

entropy changes that controls the individual values of k_M and thence the order of the stabilities. As ΔS is expected to follow the fixed order of the ionic potential of the cations, the heat changes must produce the different observed orders, and in the case of the complexes with the strong-acid anions they must therefore decrease as the ionic potential of the cation increases, *i.e.*, the energy of interaction M–H_2O must be increasingly greater than that of M–L the smaller the cation. This argument is supported (see below) by a discussion of the activity coefficients and the solubilities of the salts of the alkaline-earth cations.

No mention has been made yet of possible ion-pair formation :

$$M(H_2O)_n + L \longrightarrow M(H_2O)_nL \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Provided all the cations were equally hydrated, the expected stability of such ion-pairs would fall in the same sequence as the stability of the complexes M–L, because the size of the hydrated ions would then follow the size of the bare ions. However, it is very probable that the cations of Group IIA are decreasingly hydrated as their size increases, and so the experimentally determined stability constants might well refer to different degrees of hydration of the different cations. This difference in the nature of the "complexes" could lead to an order of stabilities opposed to the order of the ionic potential as the bare barium ion is smaller than the hydrated magnesium ion $Mg(H_2O)_6^{++}$; but this is only another expression of the fact that the ligand may not be able to displace the water of hydration from the smaller cations as easily as from the larger, and if the experimental stabilities do refer to the formation of ion pairs, $M(H_2O)$–L, of the smaller cations, their complexes, M–L, must be even less stable than is apparent. Evidence will now be discussed which would suggest that the different cations do, in fact, form "complexes" of different degrees of hydration with the strong-acid anions and that this is not so with the weak acid anions in general.

The Activity Coefficients of the Salts of the Bivalent Metal Ions.—Many of the stability constants quoted in Table 1 were obtained from consideration of the negative deviations of the activity coefficients of the corresponding salts from the theoretical values for dilute solutions as given by the Debye–Hückel equation. At higher concentrations these and other salts show positive deviations from the same equation, and this has been explained in terms of the degree of hydration of the ions by Stokes and Robinson (*J. Amer. Chem. Soc.*, 1948, **70**, 1870), who attribute a large positive deviation to a high degree of hydration, and, assuming complete dissociation, they calculate the number of water molecules associated with the ions of different salts. In this treatment no account is taken of complex or ion-pair formation, since the salts discussed are those that behave in a theoretical manner at high dilution. The theory does not explain the following points.

(*a*) The activity coefficients of the cobaltous and nickel halides are very similar to those of the magnesium halides, and yet the activity coefficients of manganous chloride lie close to those of strontium chloride, and those of copper chloride close to those of barium chloride, and the values for zinc chloride differ entirely from those of the other 2 : 1-electrolytes. All the ions of these transition metals have similar radii and yet the above treatment would lead to very different apparent hydration of these ions.

(*b*) The activity coefficients of the halides of Mg^{II}, Ca^{II}, Sr^{II}, Ba^{II}, Co^{II}, and Zn^{II} increase in the order chloride < bromide < iodide. The above authors therefore suggest an *increase* in hydration following this, the increasing order of the anionic radii. The activity coefficients of the cadmium salts increase in the opposite sequence.

(*c*) The activity coefficients of the nitrates, perchlorates, chlorides, bromides, and iodides decrease in the order Mg > Ca > Sr > Ba, at both very high and low dilution, but the activity coefficients of the weak-acid salts must decrease in the opposed order, at least in dilute solution, as shown by the stability data given on p. 3772. A similar distinction arises between the weak- and strong-acid salts of the Group IA metals (Robinson and Harned, *Chem. Reviews*, 1941, **28**, 419). Amongst the transition-metal salts of the bivalent ions there is a general order of stability of their complexes with the anions of weak acids, Mn < Fe < Co < Ni < Cu > Zn (Irving and Williams, to be published) but this order is not followed by the stability constants of the complexes or the activity coefficients of

the salts of the strong acids, *e.g.*, the chlorides and sulphates. (All these data are given by Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold, New York, 1950, 2nd edn., Chap. 13.)

Consider point (*b*): many factors would show that the hydration of the gas ions of the halogens must be in the order $Cl > Br > I$ (Bockris, *Quart. Reviews*, 1949, **3**, 173). Hence, the inverse of this order obtained by the above authors implies that their hydration values are not those of the completely dissociated salts. This is confirmed by the data on the transition-metal salts. Complex formation in the zinc halides, in the order $Cl > Br > I$, and in the cadmium halides, in the order $I > Br > Cl$, explains the negative deviations of the activity coefficients of these salts from ideal behaviour in dilute solution but also would account for the order of their positive deviations (and the resulting low apparent hydration) in concentrated solution. Cobaltous chloride is increasingly associated with increasing concentration of its solutions as determined by the change in its absorption spectrum, but cobaltous bromide is not equally associated (Job, *Ann. Chim.*, 1936, **6**, 97). This agrees with the decreasing activity coefficients of the cobaltous salts through the order $I > Br > Cl$ (Robinson, McCoach, and Lim, *J. Amer. Chem. Soc.*, 1950, **72**, 5783). The activity coefficients of magnesium chloride solution fall between those of cobaltous chloride and bromide, and it seems difficult to avoid the conclusion that the low apparent hydration of all these salts relatively to the iodides is due to association, as ion-pairs in the more dilute solutions and increasingly as complexes in the more concentrated solutions. A similar postulate would also account for the anomalous order of hydration of the halides of calcium, strontium, and barium as given by Stokes and Robinson, *i.e.*, the hydration reflects complex formation in the order $I^- < Br^- < Cl^-$.

An extension of this interpretation can be made to the activity coefficients of the oxy-acid salts in concentrated solution. In the nitrates of the Group IIA metals the activities are considerably lower than those of the corresponding chlorides, and the properties of even dilute solutions are best interpreted in terms of association (see Table 1). In the strontium and barium nitrate solutions the activity coefficients are lower than those of zinc chloride, and the variation of the coefficients with concentration suggests very low hydration consequent upon complex formation. The hydration of the smaller cations would still appear to be considerable, however. In the sulphates the activity coefficients of even the small cations are as low as the values for the cadmium halides. Now this is also the case for the sulphates of the bivalent ions of the transition metals, and the similarity in the values suggests a common property. Spectrophotometric studies in cupric sulphate solutions (Näsänen, *Acta Chem. Scand.*, 1949, **3**, 179) indicate definite complex formation. Thus it is again very probable that complex formation can take place in the salts of Group IIA metals. The fact that the order of the stability of the transition-metal sulphates is not that of the decreasing ionic radius or of the increasing ionisation potential (*i.e.*, $Mn < Fe < Co < Ni < Cu > Zn$) is a strong indication that the increments in stability of the M^{++}–SO_4^{--} bond are less than the decrements in hydration energy upon complex formation on moving from one member of this series to another of smaller radius (Irving and Williams, *loc. cit.*). The parallel with the Group IIA metals leads again to the argument of increasing *complex* formation, M–L, in the sequence $Ba > Sr > Ca > Mg$, and its further extension to the nitrates, iodates, bromates, and halides of these metals seems increasingly likely. These conclusions are in accord with the form in which the salts crystallise from solution. For instance, the barium and strontium salts of the strong acids, even the chlorides, form lattices in which the cation lies adjacent to the anion, but the magnesium salts are invariably highly hydrated, the cation being surrounded by six water molecules (Jensen, "Krystallinske Salthydrater," Nordlundes, Copenhagen, 1948). Similarly, manganous and ferrous chloride crystallise with lower hydration than cobalt and nickel chloride, whereas cupric and zinc chlorides, in solutions of which complex formation is well recognised, crystallise with only two molecules of water. In the lattice, of course, the problems of packing are more than in solution, but the following discussion illustrates some similarities between the two states of aggregation.

The Solubility of the Alkaline-earth Metal Salts.—The solubility of a salt in water is related to the stability of the corresponding complex in aqueous solution in certain circum-

stances (cf. Irving and Williams, *Nature*, 1948, **162**, 746); *e.g.*, by assuming that the lattice energy of the compound, MOx_2, a metal " oxinate " (8-hydroxyquinoline complex), was independent of the metal ion M^{++}, as any effect that this ion could produce would be screened by the large organic ligands, it was predictable that the stability of the 8-hydroxyquinoline complexes would control the order of their insolubilities: this was observed by Mellor and Maley (*Australian J. Sci. Res.*, 1949, **2**, 92). Now it is also found that the order of the insolubility of the hydroxides of these metals follows the order of the stability of the hydroxide complexes. This would apparently imply either that the lattice free energy along the series of hydroxides was constant, or even that it followed the same sequence. In these lattices, however, there is a continuous assembly. This makes an examination of the insolubility of the salts of the Group IIA metals particularly interesting, as very many of these salts crystallise in a continuous lattice. It is noteworthy that the salicylates should form a lattice of discrete molecules, in which case the insolubility and the complex stability should be directly relatable. The data so far available agree with this (Tables 1 and 5).

The solubility data are given in Table 5. The absence of any unique order is apparent, but the order obtaining is often the same as that of the complex stabilities, *e.g.*, in the hydroxides, nitrates, thiosulphates, and iodates. However, the orders are not the same in the dibasic acid salts, *e.g.*, the oxalates. It has already been pointed out that in the complexes with these ligands " crowding " effects are likely to be imposed upon the expected order of stabilities. When a lattice is built up from these ligands further co-ordination takes place in order to build a continuous assembly and simultaneously the crowding of the ligands around the central ion is increased (cf. Table 1 and Fig. 2). This should reduce in particular the stability of the magnesium lattice, and therefore explains the higher solubility of this salt than of those of the other alkaline-earth oxalates. Similar repulsion effects must appear in the fluoride lattices, *e.g.*, Pauling (*op. cit.*) considers that packing difficulties force the magnesium salt to adopt a lattice of lower co-ordination than the other fluorides. Such a low lattice stability would account for the solubility of the magnesium salt being greater than that of the calcium salt although the stabilities of their complexes are in the order Ca > Mg.

The number of water molecules of crystallisation has been mentioned as evidence of the inability of the ligand to replace water around the cation. In the strong-acid salts, such as the sulphates, nitrates, and halides, the magnesium and calcium salts are in-

TABLE 5. *Solubility of the salts of the alkaline-earth metals, solubility products,* p*S*.*

Salt	Mg	Ca	Sr	Ba	Salt	Mg	Ca	Sr	Ba
Hydroxide	11·26	5·10	3·50	2·30	Chromate	(Sol.)	3·50	4·44	9·70
Fluoride	8·19	10·41	8·52	5·77	Iodate	(Sol.)	5·71	—	8·90
Oxalate	4·07	8·64	7·25	6·96	Bromate	(Sol.)	(Sol.)	1·0	5·26
Sulphate	(Sol.)	4·64	6·55	10·00	Nitrate	(Sol.)	(Sol.)	—	2·35
Carbonate	5·00	8·32	9·03	8·31	Thiosulphate	(Sol.)	—	3·0	4·0

* $pS = -\log [M][R]^s$, where M = metal and R = anion (concentrations in g.-ions/l.)
Values taken from Latimer (" Oxidation Potentials," Prentice-Hall, New York, 1938, Appendix III).

Salt	Solubility (g./100 g. of water) Mg	Ca	Sr	Ba	Temp.
Malonate	—	0·36 (4)	0·53 (0)	0·21 (2)	20°
Succinate	24·4 (5)	1·28 (1)	0·27 (0)	0·42 (0)	20
Malate	2·5 (3)	0·92 (1)	0·55 (0)	1·24 (0)	25
(+)-Tartrate	1·2 (4)	0·04 (4)	0·18 (4)	0·30 ($\frac{1}{2}$)	25
Citrate	—	0·96 (4)	0·1 (6)	0·06 (7)	25
Salicylate	20·4 (4)	2·29 (3)	3·04 (2)	28·65 (1)	15
Acetate	39·0 (4)	34·7 (6)	41·0 ($\frac{1}{2}$)	72·0 (3)	20

All values are taken from Seidell (" Solubilities of Inorganic and Metal-Organic Compounds," 3rd edn., Van Nostrand Co., New York, 1940). The numbers in parentheses are the number of molecules of water with which the salt crystallises.

variably more hydrated than the strontium and barium salts. With the simple weak-acid salts, fluoride, hydroxide, oxalate, and carbonate, this difference does not appear. However, with the complicated anions of the hydroxy-acids, the smaller cations again crystallise with a larger number of water molecules (Table 5). The degree of hydration in

the lattice roughly parallels the solubility of the magnesium salts in a manner similar to the parallel suggested between the activity coefficients and the hydration of the salts in solution (p. 3776). Both these points can be expressed in terms of the ease of complex formation, M–L, as opposed to the formation of an ion-pair $M(H_2O)_n$–L (p. 3775).

TABLE 6. *Heats of solution (kcal./mole) of anhydrous salts.*

Salt	Mg	Ca	Sr	Ba	Salt	Mg	Ca	Sr	Ba
Acetate	—	7·00	5·56	5·24	Sulphate	20·3	5·26	—	−5·4
Formate	—	0·66	0·62	−2·44	Chloride	35·9	18·0	11·15	2·07
Glycollate	4·4	−1·62	−1·20	−5·08	Bromide	43·3	24·5	16·1	4·98
Hydroxide	1·2	3·38	10·5	11·6	Iodide	49·8	27·7	20·6	10·29
Nitrate	—	3·94	−4·7	−9·47	Sulphide	38·0	26·3	27·0	27·2

Increasing values indicate increasing tendency to dissolve. All values are taken from Bichowsky and Rossini ("Thermochemistry of Chemical Substances," Reinhold Publ. Corp., New York, 1936).

Entropy of solution (cal./°c)

Salt	Mg	Ca	Sr	Ba	Salt	Mg	Ca	Sr	Ba
Fluoride	—	−32·0	—	−25·0	Hydroxide	−55·6	−35·0	—	—
Sulphate	—	−33·0	—	−25·0	Carbonate	−60·0	−46·0	—	−38·0

Increasing negative values imply decreasing tendency to dissolve (see Rice, "Electronic Structure and Chemical Binding," Reinhold Publ. Corp., New York, 1936, Section 19·5).

The solubilities of the thiosulphates, sulphates, iodates, bromates, chromates, and nitrates, all strong-acid salts, fall in the sequence Mg > Ca > Sr > Ba. Now, the entropy of solution of the different cations would favour exactly the opposite order of solubilities, and therefore it must be assumed that the heats of solution for the salts of these cations with a given strong-acid anion are in the order of decreasing radius of the cation. The available data confirm this argument for the strong-acid salts (Table 6). For the weak-acid salts, *e.g.*, those of the monocarboxylic acids, the order is the same but the differences on moving from one cation to another are very small. In the hydroxides, the order of the heats of solution is reversed, as indeed is the order of the solubilities. In Table 6 some entropies of solution are also listed and their values can be seen to be in the order expected. The whole of this discussion is exactly paralleled by that given on p. 3774 in discussing the stability orders of the complexes with weak and strong acid anions. It should also be compared with the discussion of the solubility of Group I metal halides given by Rice (*op. cit.*, Sect. 19.5).

The above arguments, although tentative in many respects, go some way to link the stabilities of the complexes, the solubilities of the salts, and the activity coefficients of the ions of those salts in aqueous solution, especially for the Group IIA metals.

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723. *The Formation of Triarylmethylphosphonic Acids from Triarylmethylphosphonyl Dichlorides.*

By D. V. N. HARDY and H. H. HATT.

Some new *o*- and *p*-substituted triarylmethylphosphonyl dichlorides have been prepared. They are converted by alcoholic alkali partly into esters of triarylmethylphosphonic acids and partly into triarylmethyl ethers, in relative amounts depending on the substituent and the concentration of the alkali. The mechanisms of the competing reactions are deduced.

Triphenylmethylphosphonyl dichloride with alcohol gives only the ether, the presence of alkali being necessary for alcoholysis to esters of triphenylmethylphosphonic acid. If a hydroxylic compound of lower dissociating power such as methyl salicylate is used, phosphonic esters are produced in absence of alkali.

THE reaction between phosphorus trichloride and a triarylmethanol is notable, because the triarylmethyl group becomes directly attached to phosphorus giving rise to a triarylmethylphosphonyl dichloride. As alkylphosphonyl dichlorides these products are remark-

ably resistant to mild hydrolytic agents, which can therefore be used to free them of phosphorus trichloride, making their isolation in good yield particularly easy (Boyd and Chignell, *J.*, 1923, **123**, 813; Boyd and Smith, *J.*, 1926, 2323; Arbusov and Arbusov, *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 217; Hatt, *J.*, 1929, 2412; 1933, 776). Nevertheless mild hydrolytic agents slowly attack most of them, and strong hydrolytic agents such as sulphuric acid and alcoholic alkali attack them rapidly. The hydrolytic reactions are of two types: in one the chlorine atoms are replaced by hydroxyl or alkoxyl groups, giving rise to a derivative of the corresponding triarylmethylphosphonic acid; in the other the triarylmethyl and phosphonyl dichloride moieties are separated and the former is incorporated in some phosphorus-free molecule such as the triarylmethanol. The two reactions are in particularly clear competition when alcoholic alkali is the reagent; Boyd and Smith (*loc. cit.*) showed that the nature of the triarylmethyl group influenced the extent to which each reaction occurred with this reagent.

Triarylmethyl	Yields of phosphonic acid (%) With 2·5N-NaOH–EtOH	Yields of phosphonic acid (%) With 1·8N-NaOH–EtOH	Basicity of alcohol	Dissociation (%) of hexa-arylethane in 3% solution
9-Phenyl-9-fluorenyl	100	98	$\leqslant 1$	0 [a]
Triphenylmethyl	90	91	1	2·8 [b]
Diphenyl-*p*-tolylmethyl	88	86	2·3	5 [c]
Phenyldi-*p*-tolylmethyl	90	58	4	5·5 [d]
Tri-*p*-tolylmethyl	64	20	6	16 [d]
Diphenyl-*o*-tolylmethyl	59	35	1·5	25 [c], 30 [e]
o-Methoxytriphenylmethyl	26	8	1·8	3·8 [f]
α-Naphthyldiphenylmethyl	—	0 [g]	1·0	34 [e]

[a] Schlenk, Weickel, and Herzenstein, *Ber.*, 1910, **43**, 1754. [b] Preckel and Selwood, *J. Amer. Chem. Soc.*, 1941, **63**, 3397. [c] Marvel, Mueller, Himel, and Kaplan, *ibid.*, 1939, **61**, 2771. [d] Seel, F.I.A.T. Review, Theoretical Organic Chemistry, 1948, I, 89. [e] Byerly, Cutforth, and Selwood, *J. Amer. Chem. Soc.*, 1948, **70**, 1142. [f] Marvel, Whitson, and Johnston, *ibid.*, 1944, **66**, 415. [g] From Boyd and Smith, *loc. cit.*

These hydrolytic reactions have now been studied with a variety of triarylmethylphosphonyl dichlorides. At one extreme, 9-phenyl-9-fluorenylphosphonyl dichloride resists boiling ethanol, acetic acid, or aqueous alkali for hours, and with alcoholic alkali yields no alcohol or simple derivative thereof but is entirely converted into ethyl hydrogen and diethyl 9-phenyl-9-fluorenylphosphonates. At the other extreme *o*-methoxytriphenylmethylphosphonyl dichloride is hydrolysed completely to the alcohol by hot water, and with alcoholic alkali gives the ether as the main product, the amount of phosphonic acid being small unless very concentrated alkali is used. The yields of triarylmethylphosphonic acids obtained with two different concentrations of alkali are given in the annexed Table (yields were reproducible to $\pm 1\%$).

The yield of triarylmethylphosphonic acid from the phosphonyl dichloride is clearly a measure of the relative velocities of the two competing hydrolytic reactions, but it affords no measure of the relative rates of hydrolysis of different phosphonyl dichlorides. The evidence is consistent with the view that the two competing reactions are (1*a*) (S_N1 mechanism) and (2) (S_N2 mechanism).

$$R{\cdot}POCl_2 \rightleftarrows R^+ + POCl_2^- \quad . \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

$$R^+ + 2EtOH = ROEt + EtOH_2^+ \quad . \quad . \quad . \quad . \quad . \quad (1b)$$

$$R{\cdot}POCl_2 + OEt^- = R{\cdot}PClO{\cdot}OEt\ (I) + Cl^- \quad . \quad . \quad . \quad . \quad (2)$$

Supporting (1*a*) is the close resemblance of the triarylmethylphosphonyl dichlorides to the triarylchloromethanes, which shows that in many reactions they behave as carbonium salts. They give coloured solutions in dissociating solvents and form strongly coloured complexes with aluminium chloride and with stannic chloride. If the corresponding chloromethane gives a hydroxytetraphenylmethane with phenol, so also will the phosphonyl dichloride. Like the chloromethanes, with aliphatic alcohols they first form the ethers, which are then reduced to the triarylmethanes, if the solutions are sufficiently concentrated to develop high acidity by decomposition of the $POCl_2$ group.

It has been shown (Hatt, *loc. cit.*) that the first isolable intermediate in alkaline alcoholysis to the phosphonic acid or its esters is the ethyl chlorophosphinate (I). Its formation

proceeds rapidly and its subsequent conversion into the phosphonic acid or its ethyl ester proceeds quantitatively and relatively slowly. We have found that with the phosphonyl dichlorides which react readily according to (1*a*), the yield of phosphonic acid is very dependent on the concentration of alcoholic alkali. For example, with *o*-methoxytriphenylmethylphosphonyl dichloride, doubling the concentration of alkali from 1·8 to 3·6N raised the yield from 8 to 47%. Such behaviour supports the S_N2 mechanism (2).

The view that (1*a*) and (2) are the competing hydrolytic reactions accords with the order of decreasing yields of phosphonic acids from *p*-substituted phosphonyl dichlorides. Including data reported by Boyd and Smith (*loc. cit.*), the order is NO_2, Cl, H, Me, 2Me, 3Me, MeO. This order is also that of increasing alcohol basicity, of increasing conductance of the triarylchloromethanes in solution (Ziegler and Wollschitt, *Annalen*, 1930, **479**, 90; Ziegler and Mathes, *ibid.*, p. 112), and of increasing rate of chloromethane alcoholysis (Branch and Nixon, *J. Amer. Chem. Soc.*, 1936, **58**, 492). Conductances of the chloromethanes and their rates of hydrolysis have been considered as relative measures of the ease of formation of the triarylcarbonium ion and therefore also of the ease with which reaction (1*a*) occurs. It follows that the influence of the *para*-substituent on the yield of phosphonic acid can be explained entirely through its influence on reaction (1*a*). However this arrangement of the *para*-substituents in the order in which they promote reaction (1*a*) corresponds also to the arrangement of *p*-substituted benzoyl chlorides in order of their decreasing rate of alcoholysis (Branch and Nixon, *ibid.*, p. 2499). It may be that these phosphonyl dichlorides likewise enter less readily into reaction (2) in this order.

When the substituent occupies an *ortho*-position other factors must participate in controlling the yield of phosphonic acid. With *o*-methoxyphenyl, *o*-tolyl, and α-naphthyl the basicities of the alcohols are low, that of α-naphthyldiphenylmethanol being the same as triphenylmethanol (Ziegler and Boye, *Annalen*, 1927, **458**, 229; Conant and Hall, *J. Amer. Chem. Soc.*, 1927, **49**, 3062). Where measured, the conductances of the triarylchloromethanes are low (*o*-methoxyphenyl, α-naphthyl) and the rate of alcoholysis slow (α-naphthyl) and in agreement with these low basicities. Such properties would correspond in the *para*-series to 90% yields of phosphonic acids, but, instead, the yields are low and in one example nil. The basicities and allied properties show that the new effect cannot be upon reaction (1*a*). It is suggested that for *o*-tolyl and α-naphthyl the effect is one of steric opposition to the approach of the ethoxyl ion for reaction (2). These two *ortho*-groups are among the most potent in increasing the degree of dissociation of hexa-arylethanes (see table) and their influence on this property has been explained as steric in character. An explanation of this kind cannot be used for the *o*-methoxy-group, for the yield of phosphonic acid, although below that expected from its basicity and related properties, is above the yield from the *p*-methoxy-isomer. In the hexa-arylethanes also its presence appears to introduce no detectable steric effect. A single methoxyl group in either the *ortho*- or *para*-position has little stabilising influence on the triarylmethyl, but, if anything, this is greater in the *para*-position (Marvel, Whitson, and Johnson, *loc. cit.*).

If the competing hydrolytic reactions are of types (1*a*) and (2), the second should be favoured in media of low dissociating power and with their use it might be possible to obtain products from a reaction of type (2) proceeding in absence of alkali. It has been found that, whereas in alcohol (ε_{20} 25·8) little or no phosphonic acid is produced in absence of alkali, with phenol or *p*-cresol (ε_{20} 10·3) triphenylmethylphosphonyl dichloride gives appreciable quantities of the monophenyl and monotolyl esters of the acid (Boyd and Hardy, *J.*, 1928, 635). With methyl salicylate (ε_{21} 8·8) the phosphorus compounds obtained are exactly analogous to those obtained with alcohol in presence of alkali. *o*-Carbomethoxyphenyl triphenylmethylchlorophosphinate, $Ph_3C{\cdot}PClO{\cdot}O{\cdot}C_6H_4{\cdot}CO_2Me$ has been prepared in this way.

Experimental

M. p.s are not corrected.

Triarylmethanols.—9-Phenylfluoren-9-ol was prepared from fluorenone in 80% yield by reaction in ether with phenylmagnesium bromide (3 mols.). The remaining alcohols were prepared in 80—90% yield from the ethyl ester of the appropriate aromatic acid and an arylmagnesium bromide (4 mols.).

The basicities were measured by Baeyer and Villiger's method but, as recommended by Ziegler and Boye (*loc. cit.*), titration was to a faint yellow colour. Several determinations were needed to discover the desired end-point.

Triarylmethylphosphonyl Dichlorides.—The method employed was essentially that of Boyd and Chignell (*loc. cit.*), modified to suit the stability of the particular phosphonyl dichloride. To freshly distilled phosphorus trichloride (2 mols.) at 0°, the finely powdered alcohol was added in small portions with frequent shaking, during 0·5 hour, allowed to reach room temperature, and then heated for 4—5 hours at 60—70°. After cooling, the strongly coloured mixture was decomposed with crushed ice. 9-Phenyl-9-fluorenylphosphonyl dichloride is stable towards hot aqueous ammonia and hot water, and was purified by digestion with these reagents, filtration, and re-crystallization from aqueous acetone. The remaining compounds, particularly those containing *ortho*-substituents, were rapidly converted into the alcohol by these reagents and were purified by grinding them for a short time with cold dilute ammonia and with water, filtering, washing with a little light petroleum, and then drying rapidly at room temperature under reduced pressure. The pure compounds were colourless, but the less stable among them became strongly coloured in light and slowly decomposed. Their properties are tabulated.

Triarylmethylphosphonyl dichlorides.

Triarylmethyl	M. p.*	Yield (%)	Molecular formula	Found, % P	Found, % Cl	Required, % P	Required, % Cl
9-Phenyl-9-fluorenyl	153°	50	$C_{19}H_{13}OCl_2P$	8·7	19·4	8·7	19·7
Phenyldi-*p*-tolylmethyl	171·5	75	$C_{21}H_{19}OCl_2P$	8·0	18·1	8·0	18·2
Tri-*p*-tolylmethyl	177·5	75	$C_{22}H_{21}OCl_2P$	7·8	17·5	7·7	17·6
Diphenyl-*o*-tolylmethyl	124—125	60	$C_{20}H_{17}OCl_2P$	8·3	18·9	8·3	18·9
o-Methoxytriphenylmethyl ...	171·5—173·5	65	$C_{20}H_{17}O_2Cl_2P$	8·0	18·4	7·9	18·1

* Crystallisation from alcohol-free chloroform plus light petroleum (b. p. 60—80°), except for the first compound for which acetone was used.

Triarylmethylphosphonic Acids.—The general method of preparation consisted in heating the corresponding phosphonyl dichloride with 6 mols. of sodium ethoxide in alcohol according to Hatt's method (*loc. cit.*, 1929). Where the yield of phosphonic acid was not much influenced by the concentration of alkali a dilute (1·5N) reagent was used to avoid intermediate formation of the less easily hydrolysed diethyl phosphonate. Much stronger alkali (2·5 —3·0N)was used for the more easily hydrolysed phosphonyl dichlorides, in order to increase the yield of phosphonic acid. The reaction time was usually 4 hours in order to convert all intermediate phosphorus compounds into the ethyl hydrogen triarylmethylphosphonate. After the reaction, water was added in excess, the alcohol boiled off, and, when the mixture had cooled sufficiently for the insoluble by-product to coalesce, the liquid was filtered and strongly acidified with hydrochloric acid. If a quantitative estimation of the yield was required, this precipitate was collected and analysed by Hatt's method (*loc. cit.*). By careful control of conditions the yield could easily be replicated to ±1·0%.

Usually the monoethyl ester was not purified, but after drying at 100° was converted into the phosphonic acid by 1 hour's refluxing with 6 parts of 2 : 1 acetic acid–hydriodic acid (*d* 1·7). After cooling and addition of water, the precipitated phosphonic acid was filtered off, washed successively with dilute sulphurous acid, dilute hydrochloric acid, and water, dried, and crystallised.

In the preparation of 9-*phenyl*-9-*fluorenylphosphonic* acid there was no phosphorus-free by-product, but if the action of alcoholic alkali was not allowed to continue for some hours considerable amounts of diethyl 9-phenyl-9-fluorenylphosphonate were produced. In all other cases the by-product was the triarylmethyl ether if sodium ethoxide was used in absolute alcohol. The presence of water in the alcohol led to the production of triarylmethanol together with its ether, in an amount which varied considerably with the nature of the phosphonyl dichloride.

9-Phenyl-9-fluorenylphosphonic acid was prepared more conveniently by refluxing the phosphonyl dichloride for 1 hour with water (1 part) and pyridine (9 parts). Dilution with much water and acidification precipitated the phosphonic acid (90%). The method is not suitable for preparations from the more easily hydrolysed phosphonyl dichlorides.

9-*Phenyl*-9-*fluorenylphosphonic acid*. This acid crystallised from glacial acetic acid as an acetic acid *addition compound*, colourless prisms, losing acetic acid at 120° (Found : C, 66·1; H, 5·0; P, 8·1. $C_{19}H_{15}O_3P,C_2H_4O_2$ requires C, 65·9; H, 5·0; P, 8·1%). The solvent-free *acid* melts at 268° (Found : C, 70·7; H, 4·9; P, 9·5. $C_{19}H_{15}O_3P$ requires C, 70·8; H, 4·7; P, 9·6%).

The *dipotassium* salt crystallised in pearly leaflets from a solution in hot concentrated aqueous potassium hydroxide. It was collected, washed with alcohol, and dried (Found : P, 6·4; K, 16·9. $C_{19}H_{13}O_3PK_2,3H_2O$ requires P, 6·6; K, 16·6%).

Diethyl 9-phenyl-9-fluorenylphosphonate was formed as a neutral by-product in the hydrolysis of the phosphonyl dichloride with alcoholic alkali. After the action of 1·8N-alcoholic alkali had continued for 1 hour it formed 28% of the product. It crystallised from light petroleum in flat rhombs, m. p. 126° (Found : C, 73·4; H, 5·9; OEt, 23·7. $C_{23}H_{23}O_3P$ requires C, 73·0; H, 6·0; OEt, 23·2%).

Phenyl-p-tolylmethylphosphonic acid. This acid separated as an acetone *addition compound* from acetone and light petroleum (b. p. 60—80°), which readily lost the acetone at 100° (Found : loss at 100°, 13·2. $C_{21}H_{21}O_3P,C_3H_6O$ requires C_3H_6O, 14·2%). The solvent-free *acid* melted at 262—264° (Found : C, 71·4; H, 6·3; P, 8·8. $C_{21}H_{21}O_3P$ requires C, 71·6; H, 6·0; P, 8·8%). The *dipotassium* salt separated from a solution of the acid in concentrated aqueous potassium hydroxide on cooling and was obtained in small colourless needles by crystallisation from ethanol (Found : P, 5·6; K, 13·8; H_2O, 22·5 : $C_{21}H_{19}O_3PK_2,7H_2O$ requires P, 5·6; K, 14·1; H_2O, 22·7%).

Tri-p-tolylmethylphosphonic acid separated in colourless crystals [from carbon tetrachloride and light petroleum (60—80°)], m. p. 272—273° (Found : C, 71·7; H, 6·8; P, 8·4. $C_{22}H_{23}O_3P$ requires C, 72·1; H, 6·3; P, 8·4%). Its *disodium* salt separated from a solution of the acid in concentrated aqueous sodium hydroxide and crystallised from aqueous alcohol in colourless small plates (Found : P, 5·4; Na, 8·0; H_2O, 28·2. $C_{22}H_{21}O_3PNa_2,9H_2O$ requires : P, 5·4; Na, 8·0; H_2O, 28·3%).

Diphenyl-o-tolylmethylphosphonic acid separated from acetone as an *addition compound* which readily lost its acetone at 110° (Found : loss, 14·7. $C_{20}H_{19}O_3P,C_3H_6O$ requires C_3H_6O, 14·7%). The solvent-free material melted at 264° (Found : C, 71·4; H, 6·1; P, 9·2. $C_{20}H_{19}O_3P$ requires C, 71·0; H, 5·7; P, 9·3%).

o-Methoxytriphenylmethylphosphonic acid. The crude monoethyl ester obtained from the phosphonyl dichloride and alcoholic alkali was not converted into the *phosphonic acid.* The latter was obtained in 10% yield as a by-product in the preparation of the phosphonyl dichloride (cf. Boyd and Smith, 1926, *loc. cit.*), being precipitated on acidification of the ammoniacal wash-liquors. It formed colourless crystals (from glacial acetic acid), m. p. 239—240° (Found : P, 9·0. $C_{20}H_{19}O_4P$ requires P, 9·0%).

Among the ethers obtained as by-products in the formation of phosphonic acids, *ethyl o-methoxytriphenylmethyl ether* appears to be new. As the Table indicates, it was the chief product from the reaction between the corresponding triarylmethylphosphonyl dichloride and alcoholic alkali. It formed colourless parallelepipeds (from ethanol), m. p. 81° (corr) (Found : C, 83·0; H, 7·0; total alkoxyl, as MeO, 19·4. $C_{22}H_{22}O_2$ requires C, 83·0; H, 7·0; total alkoxyl, as MeO, 19·5%). The same compound was prepared from the reaction between the triarylchloromethane and alcoholic sodium ethoxide. It could not be prepared from the alcohol and alcoholic mineral acid, for even with very small concentrations of acid there was considerable reduction to the triarylmethane. A 3 : 1 mixture of sulphuric and acetic acids at 40° converted this ether into the carbonium sulphate, which was hydrolysed by water to the alcohol.

Action of Methyl Salicylate on Triphenylmethylphosphonyl Dichloride.—Triphenylmethylphosphonyl dichloride (10 g.) and pure dry methyl salicylate (20 g.) were heated at 150—160°. When the vigorous evolution of hydrogen chloride slackened, the mixture was heated for a few minutes at 200° and then cooled. Aqueous sodium carbonate was added and the unchanged methyl salicylate removed in steam. The residues were dissolved in benzene and extracted with aqueous sodium hydroxide. Acidification of the sodium hydroxide and carbonate extracts precipitated *o*-carboxyphenyl hydrogen triphenylmethylphosphonate. Evaporation of the benzene liquors and addition of ether and light petroleum gave crystals of *o*-carbomethoxyphenyl triphenylmethylchlorophosphinate. The mother-liquors from this crystallisation on evaporation left a light yellow resin which behaved as if it consisted chiefly of bis-*o*-carbomethoxyphenyl triphenylmethylphosphonate. The proportions in which these three phosphorus compounds were isolated varied considerably with small changes in the reaction conditions.

o-Carbomethoxyphenyl triphenylmethylchlorophosphinate separated from benzene or ethyl acetate in colourless crystals, m. p. 157° (Found : P, 6·7; Cl, 7·2. $C_{27}H_{22}O_4ClP$ requires P, 6·5; Cl, 7·4%). It is difficultly soluble in ether and in light petroleum, but readily soluble in benzene. It was unaffected by prolonged boiling of its solutions in alcohol and in acetic acid. Sulphuric acid dissolved it and subsequent dilution of the solution with water precipitated triphenylmethanol. Refluxing (1 hour) with an excess of N-alcoholic sodium hydroxide gave a 96% yield

of the *o*-carboxyphenyl hydrogen triphenylmethylphosphonate, isolated by the method used for ethyl hydrogen triphenylmethylphosphonate. When *o*-carbomethoxyphenyl triphenylmethylchlorophosphinate (3 g.) was boiled (1 hour) with constant-boiling hydriodic acid (1·5 ml.) and acetic acid (20 ml.) it was converted in part into triphenylmethane and in part into *o*-carboxyphenyl hydrogen triphenylmethylphosphonate, which were easily separated. Salicylic acid was also formed.

o-Carboxyphenyl hydrogen triphenylmethylphosphonate was also obtained by hydrolysis of *o*-carbomethoxyphenyl triphenylmethylchlorophosphinate or the crude bis-*o*-carbomethoxyphenyl triphenylmethylphosphonate. By all methods, after crystallisation from alcohol it was obtained as colourless crystals, m. p. 217° (Found: C, 70·0; H, 4·9; P, 7·0. $C_{26}H_{21}O_5P$ requires C, 70·3; H, 4·8; P, 7·0%). Boiling hydriodic–acetic acid slowly hydrolyses it to triphenylmethylphosphonic acid. It is dibasic and readily forms salts which crystallise well.

The *dipotassium* salt crystallised when a hot solution of the acid (1 g.) in potassium hydroxide (1·5 g.) and 80% alcohol (50 ml.) was allowed to cool. Recrystallised from 80% alcohol and air-dried, it formed colourless prisms (Found: P, 5·2; K, 13·4; H_2O, 12·2. $C_{26}H_{19}O_5PK_2,4H_2O$ requires P, 5·2; K, 13·2; H_2O, 12·2%). By double decomposition, the *barium* salt was obtained as a white precipitate, which was dried to constant weight under reduced pressure (Found: Ba, 19·9. $C_{26}H_{19}O_5PBa,6H_2O$ requires Ba, 19·9%).

The resinous material described above as probably bis-*o*-carbomethoxyphenyl triphenylmethylphosphonate (Found: P, 5·5. Calc. for $C_{35}H_{29}O_7P$: P, 5·2%) was assigned this structure because hydrolysis with potassium hydroxide in alcohol and subsequent acidification gave a theoretical yield of *o*-carboxyphenyl hydrogen triphenylmethylphosphonate together with salicylic acid. Reaction with sulphuric acid and subsequent addition of water gave triphenylmethanol. Hydriodic–acetic acid reduced it to triphenylmethane.

This work was carried out in association with Professor D. R. Boyd, whom we thank for never-failing advice and kindly criticism.

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724. *Coenzyme A. Part VI.* The Identification of Pantothenic Acid-4′ and -2′ : 4′ Phosphates from a Hydrolysate.*

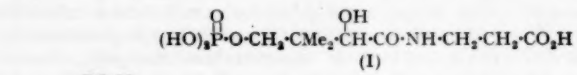
By J. Baddiley and E. M. Thain.

Cautious alkaline hydrolysis of coenzyme A gives, in addition to adenine nucleotides and 2-mercaptoethylamine, three phosphorylated derivatives of pantothenic acid. These have been isolated by the use of ion-exchange resins and chromatography on cellulose, and two of them identified as pantothenic acid-4′ and -2′ : 4′ phosphates; the third is probably the 2-mercaptoethylamide of the cyclic 2′ : 4′-phosphate. These findings support our earlier suggestions about the structure of the coenzyme.

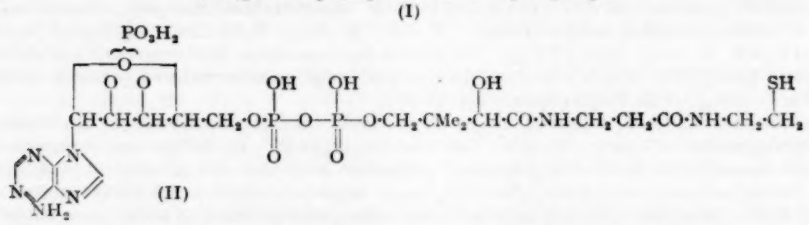
In Part II of this series (Baddiley and Thain, *J.*, 1951, 2253) it was shown that among the products of acid or alkaline hydrolysis of coenzyme A was a substance indistinguishable on paper chromatography from pantothenic acid-4′ phosphate (I). The conclusion that the synthetic 4′-phosphate was, in fact, identical with the natural product, together with more indirect supporting evidence, led us to propose the tentative structure (II) for the coenzyme. As certain microbial growth experiments (see later) were not entirely explained by this formula we considered that the actual isolation and chemical study of the pantothenic acid phosphate fragment or fragments from coenzyme A should be attempted. However, only 10 mg. of coenzyme were available for our initial experiments. Through the courtesy of Dr. F. Lipmann a somewhat larger sample of impure coenzyme has now been hydrolysed and the products separated and isolated. Although this material was not more than about 25% pure, as shown by its capacity to effect acetylation of sulphanilamide under specified

* Part V, *J.*, 1952, 800.

conditions in the presence of a liver preparation, it sufficed for our purposes. Quite impure coenzyme can be used in such experiments as those described in this paper without serious risk of obtaining invalid results provided that attention is confined to the pantothenic acid moiety and not to other parts of the molecule. This follows from the observation that all, or nearly all, of the " bound " pantothenic acid occurring in Nature is present as coenzyme A (Novelli and Schmetz, *J. Biol. Chem.*, 1951, **192**, 181). Consequently, any pantothenic acid derivatives isolated from even crude coenzyme concentrates must have originated from coenzyme A itself by hydrolytic decomposition. It was considered most probable that the low activity in the acetylation test was the result of partial hydrolysis during preparation of this sample.



(I)



(II)

Alkaline hydrolysis was effected under conditions similar to those described in Part II but the length of the hydrolysis was reduced in order to demonstrate the production of unstable intermediates. Nucleotides, adenosine, amino-acids, and other substances containing basic groups were removed together with the alkali by passage through a column of the sulphonic acid type resin " Amberlite IR-120 " in its acidic state. Paper chromatography of the resulting eluate showed that, in addition to the spot corresponding to pantothenic acid-4′ phosphate, three other organic phosphate-containing spots were present; these four products we designate A, B, C, and D in order of decreasing R_P values. By methods recorded in the Experimental section, 300 mg. of crude coenzyme A yielded 11·3 mg. of B and 9·2 mg. of C.

Substances A, B, and C were phosphates of pantothenic acid since they each gave β-alanine on acid hydrolysis. B was indistinguishable on paper chromatography in two different solvent systems from the synthetic 2′ : 4′ cyclic phosphate (III). Furthermore, like the synthetic substance it was relatively stable to acid and was hydrolysed by hot alkali to the 4′-phosphate (Part III, *J.*, 1951, 3421). Visual estimation of the relative intensities of the 2′ : 4′- and 4′-phosphate spots on paper after varying periods of hydrolysis with alkali indicated that opening of the cyclic structure occurred at the approximately same rate with both synthetic and natural cyclic phosphates. Conclusive evidence of identity of the two was obtained by a comparison of the rate of liberation of inorganic phosphate during acid hydrolysis and by infra-red spectroscopy. The curves obtained for the rate of phosphate liberation from both synthetic and natural substances were identical and differed markedly from those obtained for the 2′- and 4′-phosphates. First-order reaction kinetics were not observed. The cyclic phosphate was hydrolysed at a slower rate than was the 4′-phosphate, thereby suggesting that ring-opening and hydrolysis of the resulting phosphate occurred at comparable rates (cf. Fig. 1).

The infra-red absorption spectra of B and pantothenic acid-2′ : 4′ phosphate were indistinguishable (see Fig. 2). The small band at 13·13 μ is attributed to the presence of a slight impurity in the natural compound.

Although C was homogeneous with respect to organic phosphate it was probably impure since its infra-red absorption spectrum was ill-defined and unsuitable for comparison with that shown by the synthetic phosphates. However, it was identified as pantothenic acid-4′ phosphate from its behaviour on paper chromatography and by the fact that, like the synthetic compound, it was converted into pantothenic acid by prostate and intestinal phosphatase.

Whereas B and C were free from thiol-containing substances, A, the fastest-running product, gave a strong thiol-reaction on paper with the cyanide–nitroprusside spray. From its relatively high R_P, it seemed likely that this substance contained a di- or tri-substituted phosphate residue and this was confirmed by the observation that on further

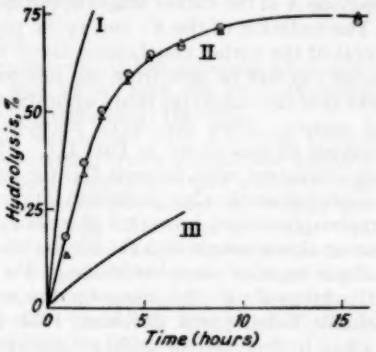


FIG. 1. *Acid hydrolysis of panothenic acid phosphates.*

I, Pantothenic acid-4′ phosphate.
II, Panothenic acid-2′ : 4′ phosphate.
⊙ Synthetic, △ From co-enzyme A.
III, Pantothenic acid-2′ phosphate.

cautious alkaline hydrolysis it was converted into pantothenic acid-2′ : 4′ phosphate together with a small amount of the 4′-phosphate. The estimated amounts present in the coenzyme A hydrolysate did not justify an attempt to isolate it in a pure state; consequently its structure could not be determined with certainty. However, on the evidence available

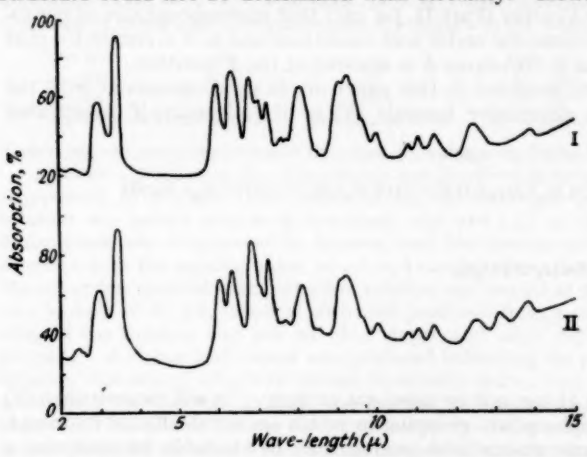


FIG. 2. *Infra-red spectra of pantothenic acid-2′ : 4′ phosphate.*

I, Synthetic.
II, From co-enzyme A.

it is probably the cyclic phosphate (IV) of pantotheine which would be expected as an early hydrolysis product of coenzyme A.

(III)

(IV)

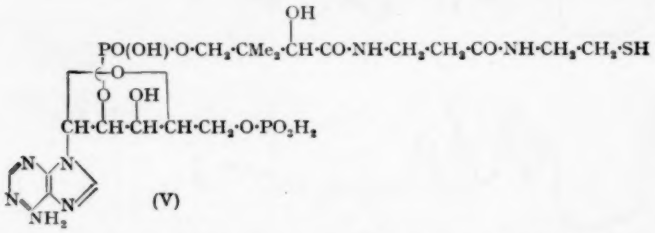
Fraction D has not yet been studied in detail. Although homogeneous with respect to phosphate its purity is not known. Whereas A, B, and C are pantothenic acid derivatives, giving β-alanine on acid hydrolysis, fraction D was free from β-alanine but in acid gave α-alanine, identified by chromatography on paper in two solvents. From the fact that it was not retained by the strongly acidic " Amberlite IR-120 " resin it is highly probable that the amino-group of the alanine residue is substituted by an acyl group. The only known

derivatives of α-alanine occurring in Nature as phosphoric esters are the uridine diphosphate nucleotides recently described by Park (*J. Biol. Chem.*, 1952, **194**, 897). The detailed structure of these substances has not yet been disclosed but it seems not unlikely that the α-alanine-containing fraction D may have arisen from similar substances accompanying coenzyme A in the earlier stages of purification.

The isolation of the 4′- and cyclic phosphates (I and III) from the coenzyme confirms several of the earlier conclusions about the structure of coenzyme A (cf. Parts II and III, *locc. cit.*) as will be seen from the following discussion. In the first place there can be no doubt that the coenzyme bears a phosphate substituent directly attached to the pantothenic acid moiety. Now the cyclic phosphate structure can not be present in the original coenzyme as was shown in Part III. The formation of a cyclic phosphate in alkali is entirely consistent with formula (II) for coenzyme A and may be visualised as having arisen through intramolecular phosphorylation. In this connection it is known that substituted pyrophosphates are powerful phosphorylating agents and a close analogy may be drawn between this example and the similar cyclisations which have been observed by the action of alkalis on other dinucleotides, *e.g.*, Forrest and Todd (*J.*, 1950, 3295) noted the formation of riboflavin-4′ : 5′ phosphate by the action of ammonia on flavin-adenine dinucleotide. Similarly, Leloir (*Arch. Biochem.*, 1951, **33**, 186) obtained a cyclic glucose phosphate from an alkali hydrolysate of uridine diphosphate-glucose.

A cyclic phosphate might arise from a structure such as (II) or from a similar structure in which the pyrophosphate linkage is attached at position 2′ (the secondary hydroxyl group) in the pantothenic acid moiety. A 2′-phosphate residue can not be present, however, since acid hydrolysis of the coenzyme gives pantothenic acid-4′ phosphate and no -2′ phosphate. It has been observed earlier (Part II, *loc. cit.*) that monophosphates of pantothenic acid show no tendency to isomerise under acid conditions and so it is concluded that the phosphate linkage in question in coenzyme A is situated at the 4′-position.

Now whereas the experiments recorded in this paper are in good agreement with the pyrophosphate formulation the alternative formula (V) or its adenosine-3′ substituted



(V)

isomer already discussed in Part II can not be ruled out entirely. It will be seen that (V) contains the disubstituted monophosphate grouping in which an unsubstituted hydroxyl, the 2′-hydroxyl group in the pantothenic acid residue, may be available for accepting a phosphate group. This structure is somewhat analogous to the ribose phosphate residues in ribonucleic acid where it has been suggested that cyclisation may precede degradation during alkaline hydrolysis (Brown and Todd, *J.*, 1952, 52). On the other hand, such a structure is unlikely in view of the very great lability of coenzyme A to alkali and acids, which is more in keeping with a pyrophosphate than a disubstituted monophosphate of this type. Contrary to earlier statements (King and Strong, *J. Biol. Chem.*, 1951, **189**, 325) Novelli has confirmed (*Phosphorus Metabolism*, 1951, **1**, 414) that coenzyme A is split by a dinucleotidase, thus proving that the coenzyme is a dinucleotide.

Pantothenic acid-4′ phosphate shows no growth promoting action towards *A. suboxydans* whereas an enzymic degradation product of coenzyme A which was stated to be free from both nucleotides and sulphur-containing substances was effective. In Part III (*loc. cit.*) we suggested that this effect might be explained by the presence in the molecule of a substituent which was essential for biological acitivity but which had so far escaped detection. If this were the correct explanation then the most probable position for this substituent

would be 2′ in the pantothenic acid residue. The ready formation of a cyclic phosphate by the action of alkali on the coenzyme, however, implies that this group must be very labile to alkali. Drs. Novelli and Lipmann have informed us, however, that their degradation product may contain sulphur and consequently it is no longer necessary to postulate the presence in the coenzyme of a substituent at the 2′ position.

Experimental

The coenzyme A used in these experiments had an activity of 110 units/mg. when assayed by the liver-enzyme method (Kaplan and Lipmann, *J. Biol. Chem.*, 1948, **174**, 37) or 43 units/mg. by bacterial arsenolysis (Stadtman, Novelli and Lipmann, *ibid.*, 1951, **191**, 365).

Hydrolysis of Coenzyme A.—Coenzyme A (300 mg.) was heated with N-sodium hydroxide (3 c.c.) at 100° for 30 minutes in a platinum tube. The resulting brown solution was heated with charcoal (*ca.* 0·1 g.) for a few minutes and filtered through kieselguhr which was then washed thoroughly with water. Sodium and basic materials were removed from the bulked filtrate and washings by passage through a column (10 × 0·5 cm.) of "Amberlite IR −120" which had been activated by repeated washing with hydrochloric acid (2N), followed by water until the eluate was free from chloride ion. The acid eluate from the column was brought to pH 10 with barium hydroxide solution and the barium phosphate removed by centrifugation. The clear supernatant liquid was freed from barium by means of another column of IR-120, and the eluate neutralised with aqueous ammonia and dried from the frozen state.

Separation of Hydrolysis Products.—The dried ammonium salts were dissolved in water (0·3 c.c.) and to the solution was added ammonia (0·9 c.c.; *d* 0·88) and *n*-propyl alcohol (1·8 c.c.), the resulting yellow solution was passed through a previously washed column of Whatman's cellulose powder (60 × 1·8 cm.) and the chromatogram developed with *n*-propyl alcohol–ammonia–water (6 : 3 : 1). Fractions (*ca.* 3 ml.) were collected and those containing phosphate were run on paper chromatograms with the same solvent, with the following results:

Tube no.	R_F		Tube no.	R_F	
24—33	0·65	A	45—56	0·23	C
34—38	0·55	B	57—80	0·1—0·05	D

R_F of pantothenic acid-2′ : 4′ phosphate, 0·55. R_F of pantothenic acid-4′ phosphate, 0·23.

Tubes whose contents possessed the same R_F value were bulked and evaporated to dryness.

Properties of Fraction A.—The residue was dissolved in water (*ca.* 0·5 c.c.), and small portions (equivalent to 0·5 mg.) were removed for the following qualitative experiments: (*a*) The solution was heated with 6N-hydrochloric acid (0·2 c.c.) at 100° (sealed tube) for 3 hours, the hydrolysate was evaporated to dryness, and the residue run on an ascending paper chromatogram with the organic phase of *n*-butyl alcohol–acetic acid–water (4 : 1 : 5). After drying, the paper was sprayed with ninhydrin solution and heated at 90° for 10 minutes. Only one spot was formed, of R_F 0·3, identical with that produced from a standard β-alanine solution. (*b*) A drop of the solution was put on filter paper and after drying sprayed with cyanide–nitroprusside. A strong pink colour was produced indicating the presence of a thiol group. (*c*) The solution was heated with 0·3N-barium hydroxide (0·2 c.c.) at 100° for 1 hour, excess of barium precipitated by carbon dioxide, the barium carbonate removed by centrifugation, barium removed from soluble barium salts by treatment with a small amount of ammonium sulphate, barium sulphate removed by centrifugation, and the clear solution evaporated to dryness. The residue was run on a paper chromatogram with *n*-propyl alcohol–ammonia and developed by the usual method. Three spots were observed: (1) unchanged fraction A, R_F 0·65, (2) a spot identical with that of pantothenic acid-2′ : 4′ phosphate, R_F 0·55, and (3) one identical with that of pantothenic acid-4′ phosphate, R_F 0·23.

Further Alkaline Hydrolysis of Fraction A.—The remainder of fraction A was heated with N-sodium hydroxide (3 c.c.) at 100° for 1 hour. Sodium ions were removed as before on Amberlite IR-120, and the acid eluate neutralised with ammonia and evaporated to dryness. The ammonium salts were separated as above on a cellulose powder column (60 × 1·1 cm.) with *n*-propyl alcohol–ammonia, fractions of 3 c.c. being collected.

Tube no.	R_F
17	0·65, unchanged fast-moving material thiol-test positive.
19—26	0·55, pantothenic acid-2′ : 4′ phosphate.
28—35	0·25, pantothenic acid-4′ phosphate.

The contents of tubes 19—26 and 28—35 were evaporated to dryness and the residues bulked with fractions B and C respectively which were further purified as below.

Purification of Fraction B.—The ammonium salt was again passed through a cellulose powder column with *n*-propyl alcohol–ammonia, and fractions (3 c.c.) were collected. Those containing substance B (as determined by a paper chromatogram) were bulked and evaporated to dryness. The residue in water (1 c.c.) was run on to a column (15 × 0·5 cm.) of Amberlite IR-4B in its acetate form. After the column had been washed with acetic acid (75 c.c., 10%) the phosphate was eluted with 3N-ammonia, fractions (3 c.c.) being collected. Those containing phosphate were bulked and evaporated to remove excess of ammonia, ammonia from ammonium salts removed by passing the solution through Amberlite IR-120 in its acid form, the acid solution evaporated to dryness four times with water to remove acetic acid, and the residual acid neutralised with barium hydroxide. The solution was heated to boiling, carbon dioxide passed to precipitate excess of barium, the slight precipitate removed by centrifugation, and the clear solution dried from the frozen state. The solid was dissolved in water (0·5 c.c.), a slight insoluble fraction removed by centrifugation, and the clear solution again dried from the frozen state, yielding the barium salt of fraction B (11·3 mg.). This fraction had the same R_F value as the synthetic pantothenic acid-2′ : 4′ phosphate in *n*-propyl alcohol–ammonia-water (R_F 0·25) and *iso*butyric acid–ammonia–water (R_F 0·50).

Identification of β-*Alanine.*—Fraction B (1 mg.) was heated with 6N-hydrochloric acid (0·2 ml.) for 3 hours at 100°, the hydrolysate was evaporated, barium removed by the addition of a little ammonium sulphate, and the residue run on a paper chromatogram in *n*-butanol–acetic acid–water, and developed with ninhydrin. A spot corresponding to β-alanine was produced (R_F 0·30).

Hydrolysis of Fraction A to Pantothenic Acid-4′ Phosphate.—Samples of pantothenic acid-2′ : 4′ phosphate and fraction B (0·5 mg.) were separately hydrolysed in 0·3N-barium hydroxide (0·2 c.c.) at 100° for 1 and 2 hours. The hydrolysates were worked up in the usual way and the products run on a paper chromatogram in *n*-propyl alcohol–ammonia. After 1 hour the cyclic phosphate and fraction A (R_F 0·50) were approximately half-converted into pantothenic acid-4′ phosphate (R_F 0·25) whilst after 2 hours this change was practically complete.

Determination of Rate of Hydrolysis of Fraction B and Pantothenic Acid-2′ : 4′ Phosphate.—The barium salts of the two phosphates (5 mg.) were separately dissolved in 2N-hydrochloric acid (10 c.c.), and aliquots (1·0 c.c.) of the solutions sealed in glass tubes. These were placed in a water-bath at 100° and individuals removed at intervals and stored at −10° until analysed. It was shown that no phosphorus was released from the glass during 24 hours' heating at 100° by this strength of acid and that the cyclic phosphate was not measurably hydrolysed at −10° over 48 hours. Phosphorus was measured colorimetrically by Allen's method (*Biochem. J.*, 1940, **34**, 858).

	Hydrolysis, %			Hydrolysis, %	
Time (hours)	Synthetic cyclic	Fraction B	Time (hours)	Synthetic cyclic	Fraction B
1	14·5	18	5·5	63·5	64·5
2	34	37	7	67	66·5
3	49	50	9	70·0	71·0
4·25	57·5	59·5	16	75·5	73·5

The greatest divergence between the figures for the synthetic cyclic phosphate and fraction B corresponds to an error of 1 μg. in the determination of phosphorus.

Purification and Properties of Fraction C.—Crude fraction C, as obtained from the cellulose column, was purified as described above for the fraction B. There was obtained a barium salt (9·2 mg.) possessing the same R_F values as pantothenic acid-4′ phosphate, in *n*-propyl alcohol–ammonia (R_F 0·25) and in *iso*butyric acid–ammonia (R_F 0·42). β-Alanine was detected in this fraction by the method given above for fraction B.

Purification and Properties of Fraction D.—The ammonium salt of fraction D was passed through a powdered cellulose column (50 × 1·5 cm.) with *n*-propyl alcohol–ammonia, fractions of 3 c.c. being collected. The fractions containing phosphorus were found by paper chromatography to contain a slow-moving organic phosphate of R_F 0·12 (same solvent); it was converted into the barium salt (20·7 mg.) by the usual method. A sample heated in 0·3N-barium hydroxide (0·2 c.c.) at 100° for 2 hours possessed unchanged R_F value in *n*-propyl alcohol–ammonia.

Acid hydrolysis of Fraction D for Amino-acids.—The barium salt of fraction D (1 mg.) was heated with 6N-hydrochloric acid (0·2 c.c.) at 100° for 3 hours, the hydrolysate evaporated to dryness, and barium removed as before. One-half of the solution was run on an ascending chromatogram in *n*-butyl alcohol–acetic acid–water along with a selection of amino-acids. On development with ninhydrin, fraction D gave a spot of R_F 0·22 corresponding to α-alanine

(R_F 0·22). The remaining half was run on a descending chromatogram in phenol saturated with water; again, fraction D gave a spot, 20 cm. from the base line, corresponding to α-alanine.

We are indebted to Dr. R. N. Haszeldine for the infra-red measurements and to the Department of Scientific and Industrial Research for a Special Research Grant.

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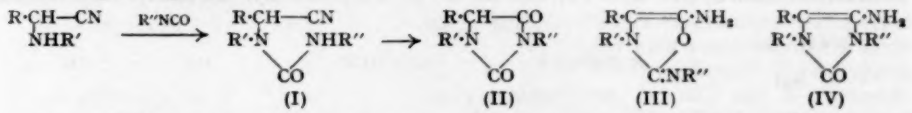
725. *Studies in the Azole Series. Part XXXIII.* The Interaction of α-Amino-nitriles and Alkyl or Aryl* iso*Cyanates.*

By A. H. COOK and G. D. HUNTER.

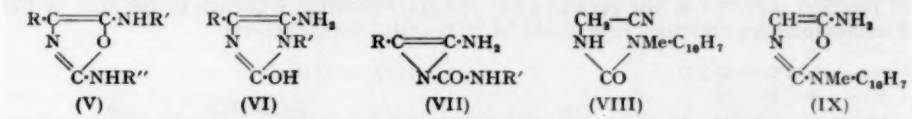
Substituted ureas obtained by the interaction of α-amino-nitriles and alkyl or aryl *iso*cyanates are converted by sodium ethoxide in ethanol into the corresponding 5-amino-oxazoles. In the case of the 5-amino-2-arylamino-oxazoles, treatment with aqueous sodium hydroxide results in the formation of dimeric products—obtained in some cases directly in admixture with 5-amino-oxazoles—which are formulated as 1-arylcarbamyl-3-*N'*-arylureido-2 : 4-di-imino-pyrrolidines.

ALTHOUGH the interaction of α-amino-nitriles and various organic *iso*thiocyanates has been discussed in earlier Parts of this series (Cook, Downer, and Heilbron, *J.*, 1948, 1262, 2028; Capp, Cook, Downer, and Heilbron, *J.*, 1948, 1340; Cook, Heilbron, and Smith, *J.*, 1949, 1140), little has hitherto been reported on reactions involving α-amino-nitriles and organic *iso*cyanates apart from the formation of substituted ureas (I) (Pinner and Lifschütz, *Ber.*, 1887, **20**, 2355; Pinner, *Ber.*, 1888, **21**, 2321; Mouneyrat, *Ber.*, 1900, **33**, 2393; Klages, *J. pr. Chem.*, 1902, [ii], **65**, 189; Delepine, *Bull. Soc. chim.*, 1903, **29**, 1190, 1198; Cook, Downer, and Heilbron, *J.*, 1948, 1264) and certain of the corresponding hydantoins (II). The present work shows, however, that compounds of type (III) are readily obtainable from the corresponding ureas (I).



(I) (II) (III) (IV)

The reaction between ethyl aminocyanoacetate and α-naphthyl and phenyl *iso*cyanates yielded respectively *N*-carbethoxycyanomethyl-*N'*-α-naphthyl- and -*N'*-phenyl-urea (I; R = CO_2Et, R' = H, R'' = $C_{10}H_7$ or Ph respectively). As expected, the former urea was readily converted into 5-carbethoxy-3-α-naphthylhydantoin (II; R = CO_2Et, R' = H, R'' = $C_{10}H_7$) by acid. Each of the ureas, however, was converted into a compound isomeric with the starting material when heated under reflux with ethanolic sodium ethoxide. For reasons given below, these isomers have been assigned the structures ethyl 5-amino-2-α-naphthylamino- and 5-amino-2-anilino-oxazole-4-carboxylate (V; R = CO_2Et, R' = H, R'' = $C_{10}H_7$ or Ph respectively). The former 5-amino-oxazole formed a crystalline



(V) (VI) (VII) (VIII) (IX)

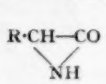
monohydrochloride, a monomethyl derivative (probably V; R = CO_2Et, R' = Me, R'' = $C_{10}H_7$), and a monoacetyl derivative (V; R = CO_2Et, R' = Ac, R'' = $C_{10}H_7$). Its alternative formulation as 5-amino-2-hydroxy-1-α-naphthylglyoxaline was rendered most unlikely, first by its failure to couple with diazonium salts under a variety of conditions, and secondly by the failure of attempts to hydrolyse it to the corresponding hydantoin.

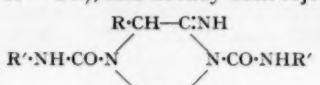
Similarly interaction of aminoacetonitrile and α-naphthyl *iso*cyanate in ether yielded *N*-cyanomethyl-*N'*-α-naphthylurea (I; R = R' = H, R'' = $C_{10}H_7$) which was smoothly

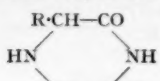
* Part XXXII, *J.*, 1950, 1898.

converted into 3-α-naphthylhydantoin (II; R = R′ = H, R″ = $C_{10}H_7$) and also into 5-amino-2-α-naphthylamino-oxazole (V; R = R′ = H, R″ = $C_{10}H_7$), which formed a hydrochloride but was not diazotised under any of the usual conditions. The only possible alternative structures appeared to be those of the 5-aminoglyoxaline (VI; R = H, R′ = $C_{10}H_7$) and the 2-aminoazirine (VII; R = H, R″ = $C_{10}H_7$). The latter unlikely possibility was eliminated, for *N*-cyanomethyl-*N*-methyl-*N*′-α-naphthylurea (I, R = H, R′ = Me, R″ = $C_{10}H_7$) readily gave an isomeric product, 5-amino-2-α-naphthylimino-3-methyl-4-oxazoline (III; R = H, R′ = Me, R″ = $C_{10}H_7$), an azirine structure being impossible. 1-Methyl-3-α-naphthylhydantoin was readily obtained from the corresponding urea, as with the lower homologue. *N*-Cyanomethyl-*N*′-α-naphthylurea afforded a monomethyl derivative which was not identical with the isomer (I; R = H, R′ = Me, R″ = $C_{10}H_7$) previously obtained, and was evidently *N*-cyanomethyl-*N*′-methyl-*N*′-α-naphthylurea (VIII). Treatment with sodium ethoxide afforded an isomer which must have been 5-amino-2-(*N*-methyl-α-naphthylamino)-oxazole (IX), since this time a 5-aminoglyoxaline formulation was impossible.

Light was thrown on the structure of several compounds obtained incidentally (see Experimental section) largely as a result of investigations carried out on corresponding compounds derived from α-aminobenzyl cyanide. The latter substance readily gave, with α-naphthyl *iso*cyanate, *N*-α-cyanobenzyl-*N*′-α-naphthylurea (I; R = Ph, R′ = H, R″ = $C_{10}H_7$) which was converted by acid hydrolysis into 3-α-naphthyl-5-phenylhydantoin (II; R = Ph, R′ = H, R″ = $C_{10}H_7$), characterised as its monomethyl derivative. Treatment with sodium ethoxide under the usual conditions gave rise to two products, each isomeric with the starting material. The one formed in smaller proportion was regarded as 5-amino-2-α-naphthylamino-4-phenyloxazole (V; R = Ph, R′ = H, R″ = $C_{10}H_7$); it was characterised as a monohydrated monomethyl derivative, probably (V; R = Ph, R′ = Me, R″ = $C_{10}H_7$). It was easily convertible into the second isomer by boiling aqueous sodium hydroxide, and hydrolysis with ethanolic hydrogen chloride led to the formation of a compound of empirical formular C_8H_7ON. As a three-membered ring formulation, such as (X; R = Ph), had already been rejected in a case above, these results

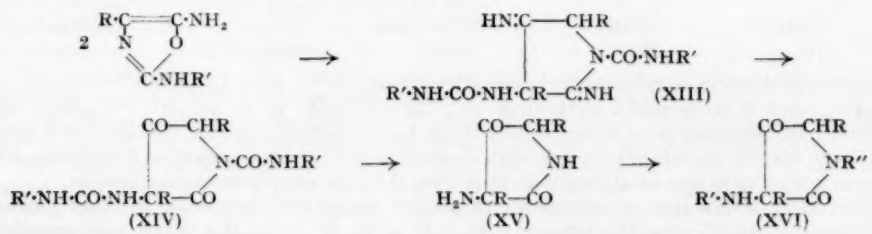

(X)


(XI)


(XII)

could only be interpreted on the basis that the compounds described here were dimeric and this indeed proved to be the case for the compound having the empirical formula C_8H_7ON. Di-imino- (XI) and diketo-piperazine (XII) structures were dismissed on account of the non-identity of the compound obtained in the present work with the known 2 : 4-diketo-3 : 5-diphenylpiperazine.

The compounds described here bore analogies to the " dibenzamidodioxytetrol " (Rügheimer, *Ber.*, 1888, **21**, 3325; 1889, **22**, 1954) which Cornforth and Huang (*J.*, 1948, 1958) have shown to be 3-benzamido-1-benzoyl-2 : 4-diketopyrrolidine. If the same type of reaction occurred in the present case, the corresponding sequence in the case of the 5-amino-oxazoles described here would be represented by the scheme :


(XIII) (XIV) (XV) (XVI)

Subsequent experiments have confirmed with reasonable certainty that this scheme

indeed describes the processes under investigation. The isomer obtained together with 5-amino-2-α-naphthylamino-4-phenyloxazole was formulated as 2 : 4-di-imino-1-α-naphthylcarbamyl-3-*N'*-α-naphthylureido-3 : 5-diphenylpyrrolidine (XIII; R = Ph, R' = $C_{10}H_7$), and the hydrolysis product $(C_8H_7ON)_2$ as 2 : 4-diketo-3 : 5-diphenylpyrrolidine (XV; R = Ph). Methylation confirmed the latter structure, a monomethyl derivative, presumably 3-amino-2 : 4-diketo-1-methyl-3 : 5-diphenylpyrrolidine (XVI; R = Ph, R' = H, R'' = Me) being obtained, while acetylation gave rise to a diacetyl derivative, presumably (XVI; R = Ph, R' = R'' = H). The compound (XV; R = Ph) moreover gave a red ferric chloride colour (cf. the colours obtained by Cornforth and Huang, *loc. cit.*, with similar compounds). The parent pyrrolidine (XIII; R = Ph, R' = $C_{10}H_7$) in its turn was characterised by a tetramethyl derivative and a diacetyl derivative. Reaction of the original 5-amino-oxazole (V; R = Ph, R' = H, R'' = $C_{10}H_7$) with ethanolic hydrogen chloride gave two further products whose composition was also in conformity with the above scheme: one was evidently 2 : 4-diketo-1-α-naphthylcarbamyl-3-*N'*-α-naphthylureido-3 : 5-diphenylpyrrolidine (XIV; R = Ph, R' = $C_{10}H_7$) while the other was undoubtedly the ethochloride of (XV; R = Ph). In view of these results, certain compounds obtained incidentally in other series (see Experimental section) have also been formulated as pyrrolidines.

In addition to the above testimony in favour of pyrrolidine structures, indirect evidence was obtained from a study of certain 5-amino-3-methyloxazolines. As was expected, 5-amino-3-methyl-2-α-naphthylimino-oxazoline (III; R = H, R' = Me, R'' = $C_{10}H_7$) gave no isomer in boiling alkali. A similar result was obtained in a further case where α-methylamino-*n*-valeronitrile was converted into *N*-1-cyano-*n*-butyl-*N*-methyl-*N'*-α-naphthylurea (I; R = Pr^n, R' = Me, R'' = $C_{10}H_7$) and thence into the isomeric 5-amino-3-methyl-2-α-naphthylimino-3-*n*-propyloxazoline (III; R = Pr^n, R' = Me, R'' = $C_{10}H_7$) in the usual way. 1-Methyl-3-α-naphthyl-5-*n*-propylhydantoin (II; R = Pr^n, R' = Me, R'' = $C_{10}H_7$), obtained from the above substituted urea by acid hydrolysis, had previously been prepared by the action of α-naphthyl *iso*cyanate on α-methylamino-*n*-valeric acid (Friedmann, *Beitr. Chem. Physiol. Path.*, 1908, **11**, 172).

In order to establish the generality of these reactions, further experiments were carried out with other *iso*cyanates. Phenyl *iso*cyanate reacted readily with α-aminobenzyl cyanide and α-methylamino-*n*-valeronitrile, yielding respectively *N*-α-cyanobenzyl-*N'*-phenylurea (I; R = R'' = Ph, R' = H) (Cook, Downer, and Heilbron, *loc. cit.*) and *N*-α-cyano-*n*-butyl-*N*-methyl-*N'*-phenylurea (I; R = Pr^n, R' = Me, R'' = Ph). The former compound behaved as was expected in that, after its treatment with sodium ethoxide in dry ethanol, 5-amino-2-anilino-4-phenyloxazole (V; R = R'' = Ph, R' = H) was ultimately isolated (as its acetate), together with a much larger proportion of the corresponding 2 : 4-di-iminopyrrolidine (XIII; R = R' = Ph).

Attention was then turned to the products derived from methyl *iso*cyanate, which reacted with α-aminobenzyl cyanide and with ethyl aminocyanoacetate, giving *N*-α-cyanobenzyl-*N'*-methylurea (I; R = Ph, R' = H, R'' = Me) and *N*-carbethoxycyanomethyl-*N'*-methylurea (I; R = CO_2Et, R' = H, R'' = Me) respectively. Hydrolysis of the former urea led to 3-methyl-5-phenylhydantoin (II; R = Ph, R' = H, R'' = Me), previously obtained by methylation of 5-phenylhydantoin (Pinner, *Ber.*, 1888, **21**, 2325). Cyclisation of the same urea gave only one isomer which was designated as 5-amino-2-methylamino-4-phenyloxazole (V; R = Ph, R' = H, R'' = Me). This compound could not, however, be isomerised further, as, when warmed with alkali, it rapidly lost methylamine. Ethyl aminocyanoacetate and α-aminobenzyl cyanide afforded *N*-carbethoxycyanomethylurea (I; R = CO_2Et, R' = R'' = H) and *N*-α-cyanobenzylurea (I; R = Ph, R' = R'' = H) (Pinner and Lifschütz, *loc. cit.*) respectively. Treatment of the latter urea with sodium ethoxide in dry ethanol led to extensive decomposition and only to a small yield of 2 : 5-diamino-4-phenyloxazole (V; R = Ph, R' = R'' = H). These results suggest that the transformation of a 5-amino-oxazole into a 2 : 4-di-iminopyrrolidine as described above is a property confined to those oxazoles carrying a 2-arylamino-substituent, though it is emphasised that the corresponding 2-alkylamino-compounds have so far only received limited study.

Experimental

Compounds derived from Ethyl Aminocyanoacetate and α-Naphthyl iso*Cyanate.*—Ethyl aminocyanoacetate (25·0 g.) in ether (150 c.c.) was stirred at 0° while a solution of α-naphthyl *iso*cyanate (33·0 g.) in ether (150 c.c.) was added during 15 minutes. The bulky colourless precipitate of N-*carbethoxycyanomethyl*-N′-α-*naphthylurea* (58·0 g., 100%) was collected after 24 hours at 0°; it crystallised from ethanol in masses of small needles, m. p. 179° (Found: C, 64·9; H, 5·3; N, 14·3. $C_{16}H_{15}O_3N_3$ requires C, 64·7; H, 5·1; N, 14·1%). The urea (1·0 g.) was heated under reflux with 10% ethanolic hydrogen chloride (10 c.c.) for 1 hour, passing rapidly into solution and being replaced by a precipitate of ammonium chloride. Filtration and addition of water (60 c.c.) to the filtrate yielded 5-*carbethoxy*-3-α-*naphthylhydantoin* (0·9 g., 90%), which crystallised from aqueous methanol in colourless prisms, m. p. 85° (Found: N, 9·1. $C_{16}H_{14}O_4N_2$ requires N, 9·4%). N-*Carbethoxycyanomethyl*-N′-α-*naphthylurea* (35·0 g.) was heated under reflux with a solution of sodium ethoxide [from sodium (2·6 g.) in dry ethanol (200 c.c.)] for 2 hours, and the deep yellow solution evaporated to dryness *in vacuo*. The crystalline residue was suspended in ice-cold water (100 c.c.) and acidified with acetic acid. The precipitate of *ethyl* 5-*amino*-2-α-*naphthylamino-oxazole*-4-*carboxylate* (33·0 g., 94%) was crystallised from aqueous acetic acid in rosettes of prisms, m. p. 237° (decomp.) [Found: C, 64·7; H, 5·2; N, 13·9%; *M* (Rast), 314, 312. $C_{16}H_{15}O_3N_3$ requires C, 64·7; H, 5·1; N, 14·1%; *M*, 297]. The above 5-amino-oxazole (0·5 g.) was added to 10% ethanolic hydrogen chloride (5 c.c.), whereupon it rapidly passed into solution. Filtration and addition of ether (30 c.c.) yielded, after 24 hours at 0°, *ethyl* 5-*amino*-2-α-*naphthylamino-oxazole*-4-*carboxylate hydrochloride* (0·5 g.) in masses of colourless rods or prisms, m. p. 215° (Found: C, 57·7; H, 5·1; N, 12·1. $C_{16}H_{15}O_3N_3Cl$ requires C, 57·8; H, 4·8; N, 12·6%). The same amino-oxazole yielded a *monomethyl* derivative when treated with diazomethane in ether; this crystallised from aqueous methanol in pale yellow felted needles, m. p. 98° (decomp.) (Found: N, 13·8. $C_{17}H_{17}O_3N_3$ requires N, 13·5%). Ethyl 5-amino-2-α-naphthylamino-oxazole-4-carboxylate (0·8 g.) was heated under reflux with acetic anhydride (5 c.c.) for 5 minutes, and the solution evaporated to dryness *in vacuo*. Extraction with methanol and addition of water to the extract yielded *ethyl* 5-*acetamido*-2-α-*naphthylamino-oxazole*-4-*carboxylate* (0·1 g.), which crystallised from ethanol–water in small pale yellow prisms of the *monohydrate*, m. p. 100° (Found: N, 11·7. $C_{18}H_{17}O_4N_3,H_2O$ requires N, 11·8%).

Ethyl 5-amino-2-α-naphthylamino-oxazole-4-carboxylate (10·0 g.) was heated under reflux with 10% aqueous sodium hydroxide (100 c.c.) until it dissolved (*ca.* 25 minutes). α-Naphthylamine was deposited and the suspension was cooled to 0°, then filtered, and the filtrate acidified with acetic acid. After 48 hours at 0°, the yellow precipitate of *diethyl* 2 : 4-*di-imino*-1-α-*naphthylcarbamyl*-3-N′-α-*naphthylureidopyrrolidine*-3 : 5-*dicarboxylate* (6·0 g., 60%), m. p. *ca.* 145° (decomp.), was filtered off and crystallised from acetic acid–water in yellow felted needles (Found: C, 64·8; H, 5·1; N, 13·8. $C_{32}H_{30}O_6N_6$ requires C, 64·7; H, 5·1; N, 14·1%). This pyrrolidine (3·0 g.) was heated under reflux with 10% ethanolic hydrogen chloride (30 c.c.) for 1 hour and the solution obtained poured into cold water (200 c.c.) and cooled to 0° for 48 hours. Filtration, extraction of the precipitate with methanol (10 c.c.), and further precipitation with water (30 c.c.) yielded 2 : 4-*diketo*-1-*naphthylcarbamyl*-3-N′-α-*naphthylureidopyrrolidine monohydrate* (1·0 g.), m. p. 80—110° (decomp.) (Found: C, 66·1; H, 4·7; N, 12·3. $C_{26}H_{22}O_5N_4$ requires C, 66·4; H, 4·7; N, 11·9%). Ethyl 5-amino-2-α-naphthylamino-oxazole-4-carboxylate (1·3 g.) was heated under reflux with 10% ethanolic hydrogen chloride (10 c.c) for 3 hours and poured into cold water (50 c.c.). The product obtained after 12 hours at 10° was a complex mixture, but fractional crystallisation from methanol–water led to the isolation of *diethyl* 3-*amino*-2 : 4-*diketopyrrolidine*-3 : 5-*dicarboxylate* in small golden prisms, m. p. 125° (decomp.) (Found: C, 45·6; H, 5·0; N, 11·8. $C_{10}H_{14}O_6N_2$ requires C, 46·5; H, 5·4; N, 10·9%).

Compounds derived from α-Aminobenzyl Cyanide and α-Naphthyl iso*Cyanate.*—A solution of α-naphthyl *iso*cyanate (33·8 g.) in ether (100 c.c.) was added during 20 minutes to a stirred solution of α-aminobenzyl cyanide (26·4 g.) in ether (250 c.c.) at 0°. The exothermic reaction rapidly produced a voluminous white precipitate of N-α-*cyanobenzyl*-N′-α-*naphthylurea* (58·5 g., 97%), which was collected after 24 hours at 0°. The urea crystallised from acetic acid in needles, m. p. 190° (decomp.) (Found: C, 75·8; H, 5·1; N, 14·3. $C_{19}H_{15}ON_3$ requires C, 75·8; H, 5·0; N, 14·0%). This urea (2·0 g.) was heated under reflux with 10% ethanolic hydrogen chloride (20 c.c.) for 75 minutes. Ammonium chloride was filtered off, and addition of water (50 c.c.) to the filtrate precipitated 3-α-*naphthyl*-5-*phenylhydantoin* (1·8 g., 90%) which crystallised from methanol in short colourless needles, m. p. 192° (Found: C, 75·7; H, 4·9; N, 9·4. $C_{19}H_{14}O_2N_2$ requires C, 75·5; H, 4·6; N, 9·3%). Acetylation of the hydantoin with

boiling acetic anhydride in presence of a trace of sulphuric acid gave a *monoacetyl* derivative which crystallised from acetic acid in silvery rods, m. p. 201° (Found, C, 73·6; H, 4·7; N, 8·1. $C_{21}H_{16}O_3N_2$ requires C, 73·3; H, 4·7; N, 8·1%).

N-α-Cyanobenzyl-*N'*-α-naphthylurea (45·0 g.) was heated under reflux with a solution of sodium (3·6 g.) in dry ethanol (250 c.c.) for 2 hours, and the yellow solution evaporated to dryness *in vacuo*. The crystalline residue was suspended in water (150 c.c.) and neutralised with acetic acid. After cooling at 0° for 12 hours, the yellow precipitate (45·0 g.) was filtered off and dried over calcium chloride *in vacuo*. Extraction with hot methanol left the sparingly soluble *5-amino-2-α-naphthylamino-4-phenyloxazole* (18·0 g., 40%), which crystallised from acetic acid in small colourless prisms, m. p. 261° (Found: C, 75·6; H, 5·0; N, 14·0. $C_{19}H_{15}ON_3$ requires C, 75·8; H, 5·0; N, 14·0%). Crystallised from dioxan, it formed a stable *compound*, m. p. 257° (decomp.), as colourless needles and prisms which were no longer soluble in dioxan (Found: C, 72·2; H, 5·9; N, 11·6. $4C_{19}H_{15}ON_3,3C_4H_8O_2$ requires C, 71·9; H, 5·7; N, 11·4%). Addition of water to the methanolic filtrates (200 c.c.) obtained above yielded a pale yellow precipitate of *2:4-di-imino-1-α-naphthylcarbamyl-3-N'-α-naphthylureido-3:5-diphenylpyrrolidine* (26·5 g., 59%), which crystallised from aqueous methanol in colourless prisms (Found: C, 75·8; H, 4·9; N, 13·6. $C_{38}H_{30}O_2N_6$ requires C, 75·8; H, 5·0; N, 14·0%). On being heated, it gradually melted in the range 125—135° with effervescence which subsided at 160°, the compound then resolidifying. When heated further, it had m. p. 230—235° (decomp.). 5-Amino-2-α-naphthylamino-4-phenyloxazole with diazomethane in ether formed a *monomethyl* derivative, pale yellow prisms (from aqueous methanol), m. p. 95° (decomp.) (Found: N, 12·8. $C_{20}H_{17}O_2N_3$ requires N, 12·6%). 2:4-Di-imino-1-α-naphthylcarbamyl-3-N'-α-naphthylureido-3:5-diphenylpyrrolidine (1·0 g.) was covered with a solution of diazomethane (1·0 g.) in ether (30 c.c.); nitrogen was evolved and the solution was allowed to evaporate to dryness. The *tetramethyl* derivative crystallised from aqueous methanol in masses of small pale yellow prisms of the *solvate*, m. p. 97° (decomp.) (Found: C, 73·5; H, 6·0; N, 11·6. $C_{42}H_{38}O_2N_6,2CH_3{\cdot}OH$ requires C, 73·1; H, 6·4; N, 11·6%). The compound was very sensitive to heat, and it was not possible to dry it above room temperature or remove the methanol of crystallisation without extensive decomposition. The same pyrrolidine formed a *diacetyl* derivative when boiled with an excess of acetic anhydride for a few minutes, crystallising from aqueous pyridine in clusters of small colourless prisms, m. p. 258° (decomp.) (Found: N, 12·4. $C_{42}H_{34}O_4N_6$ requires N, 12·2%). 5-Amino-2-α-naphthylamino-4-phenyloxazole (2·0 g.) was heated under reflux with 10% ethanolic hydrogen chloride (20 c.c.) for 4 hours. The solution was filtered and cooled to 0°. Addition of water (50 c.c.) then precipitated *2:4-diketo-1-α-naphthylcarbamyl-3-N'-α-naphthylureido-3:5-diphenylpyrrolidine* (1·0 g.) as a yellow solid. Crystallisation from methanol–water at 0° gave pale yellow prisms, m. p. 145—155° (decomp.) (Found: C, 76·4; H, 5·5; N, 9·4. $C_{38}H_{28}O_4N_4$ requires C, 75·5; H, 4·7; N, 9·3%). Purification was very difficult as the product appeared to decompose in the presence of most organic solvents and probably contained appreciable quantities of further degradation products.

2:4-Di-imino-1-α-naphthylcarbamyl-3-*N'*-α-naphthylureido-3:5-diphenylpyrrolidine (5·0 g.) was heated under reflux with 10% ethanolic hydrogen chloride (50 c.c.) for 1 hour. After filtration, addition of water (200 c.c.), and cooling to 0° for 12 hours, the pale yellow precipitate of *3-amino-2:4-diketo-3:5-diphenylpyrrolidine* (2·0 g.) was collected. It crystallised from aqueous methanol in colourless prisms, m. p. 174° (decomp.) (Found: C, 72·3; H, 5·1; N, 10·9%; *M*, 310. $C_{16}H_{14}O_2N_2$ requires C, 72·2; H, 5·3; N, 10·5%; *M*, 266). This last pyrrolidine (1·0 g.) was covered with a solution of diazomethane (0·5 g.) in ether (30 c.c.) and the ether allowed to evaporate slowly. The residual *3-amino-2:4-diketo-1-methyl-3:5-diphenylpyrrolidine* (1·0 g.) crystallised from aqueous methanol in pale yellow felted needles, m. p. 198° (decomp.) (Found: C, 72·5; H, 5·5; N, 10·0. $C_{17}H_{16}O_2N_2$ requires C, 72·9; H, 5·7; N, 10·0%). The same aminodiketodiphenylpyrrolidine was treated with boiling acetic anhydride for 2 minutes. Working up in the usual manner gave *1-acetyl-3-acetamido-2:4-diketo-3:5-diphenylpyrrolidine* as a colourless solid which crystallised from ethanolic acetic acid in colourless rectangular plates, m. p. 215° (Found: C, 68·2; H, 4·6. $C_{20}H_{18}O_4N_2$ requires C, 68·6; H, 5·1%). 5-Amino-2-α-naphthylamino-4-phenyloxazole (0·2 g.) was dissolved in cold 10% ethanolic hydrogen chloride (10 c.c.). Ether (120 c.c.) and light petroleum (b. p. 40—60°) (20 c.c.) were added, and the filtered solution was set aside at 0° for 2 weeks. Large colourless rectangular plates of *3-amino-1:1-diethyl-2:4-diketo-3:5-diphenylpyrrolidinium chloride* (0·1 g.), m. p. 245—255° (decomp.), were filtered off (Found: C, 65·3; H, 5·8; N, 8·5. $C_{19}H_{19}O_2N_2Cl$ requires C, 65·4; H, 5·8; N, 8·5%).

Compounds derived from other α-Amino-nitriles and α-Naphthyl iso*Cyanate.*—α-Naphthyl *iso*-

cyanate (39·0 g.) in ether (150 c.c.) was added to a stirred solution of aminoacetonitrile (13·0 g.) in chloroform (60 c.c.) at 0° during 15 minutes. The exothermic reaction rapidly produced a voluminous white precipitate of *N-cyanomethyl-N′-α-naphthylurea* (51·5 g., 99%) which was collected after 24 hours at 0°. It crystallised from methanol in masses of colourless needles, m. p. 183° (Found : C, 69·3; H, 4·9; N, 18·4. $C_{13}H_{11}ON_3$ requires C, 69·3; H, 4·9; N, 18·7%). The above urea (1·0 g.) was converted by boiling 10% ethanolic hydrogen chloride into *3-α-naphthylhydantoin* (0·9 g.) which crystallised from methanol in large colourless rhombs, m. p. 219° (Found : N, 12·7. $C_{13}H_{10}O_2N_2$ requires N, 12·4%). *N*-Cyanomethyl-*N′*-α-naphthylurea (30·0 g.) was added to a solution of sodium ethoxide [from sodium (3·4 g.) in dry ethanol (200 c.c.)] and heated under reflux for 1·5 hours. Evaporation to dryness *in vacuo* yielded a colourless crystalline solid which was suspended in water (150 c.c.) and neutralised with acetic acid. The precipitate of *5-amino-2-α-naphthylamino-oxazole* (30·0 g., 100%) crystallised from methanol in plates, m. p. 193° (decomp.)(Found: C, 69·3; H, 5·1; N, 18·7. $C_{13}H_{11}ON_3$ requires C, 69·3; H, 4·9; N, 18·7%). The compound gradually decomposed when heated in camphor (Rast) (Found : *M*, 281. $C_{13}H_{11}ON_3$ requires *M*, 225). The above oxazole (1·0 g.) was shaken with 10% ethanolic hydrogen chloride (10 c.c.) at room temperature; it rapidly passed into solution and was replaced by a colourless precipitate of *5-amino-2-α-naphthylamino-oxazole hydrochloride* (1·1 g.) which was collected after 1 week at 0° and crystallised from methanol–ether in colourless rods, m. p. 217° (decomp.) (Found : C, 59·9; H, 4·9; N, 15·7. $C_{13}H_{12}ON_3Cl$ requires C, 59·7; H, 4·6; N, 16·1%).

5-Amino-2-α-naphthylamino-oxazole (10·0 g.) was suspended in 10% aqueous sodium hydroxide (100 c.c.) and warmed to 80°; the oxazole rapidly passed into solution and was replaced by a bulky precipitate of α-naphthylamine. Heating was continued for 5 minutes before cooling to 0° and removal of α-naphthylamine by filtration. The filtrate was acidified with acetic acid and kept at 0° for 24 hours. *2 : 4-Di-imino-1-α-naphthylcarbamyl-3-N′-α-naphthylureidopyrrolidine* (0·8 g., 8%) was collected and crystallised from aqueous methanol in yellow felted needles, m. p. 161—163° (decomp.) (Found : C, 68·8; H, 5·0; N, 18·7. $C_{26}H_{22}O_2N_6$ requires C, 69·3; H, 4·9; N, 18·7%).

N-Methylaminoacetonitrile (7·0 g.) in ether (300 c.c.) was stirred at 0° while a solution of α-naphthyl *iso*cyanate (17·0 g.) in ether (100 c.c.) was added during 10 minutes. The colourless precipitate of *N-cyanomethyl-N-methyl-N′-α-naphthylurea* (20·5 g., 85%) was collected after 24 hours at 0°, and crystallised from benzene, forming long, thin needles, m. p. 126° (Found : C, 70·4; H, 5·6; N, 17·9. $C_{14}H_{13}ON_3$ requires C, 70·3; H, 5·4; N, 17·6%). Heating this compound under reflux with 10% ethanolic hydrogen chloride for 2 hours gave *1-methyl-3-α-naphthylhydantoin*, massive, irregular colourless prisms, m. p. 183 (from methanol) (Found : N, 11·9. $C_{14}H_{12}O_2N_2$ requires N, 11·7%). The same urea (12·0 g.) was heated under reflux for 1·5 hours with a solution of sodium ethoxide [from sodium (1·2 g.)] in dry ethanol. The solution was evaporated to dryness *in vacuo*, the residue suspended in water (50 c.c.) and neutralised with acetic acid, and the precipitate collected after 6 hours at 0°. *5-Amino-3-methyl-2-α-naphthyliminooxazoline* (10·0 g., 83%) crystallised from methanol in thin rectangular plates, m. p. 163° (Found : C, 70·7; H, 5·7; N, 17·3. $C_{14}H_{13}ON_3$ requires C, 70·3; H, 5·4; N, 17·6%). After being boiled with 10% aqueous sodium hydroxide for a short period, it was recovered unchanged on acidification, though in small yield.

N-Cyanomethyl-*N′*-α-naphthylurea (5·0 g.) and methyl sulphate (3·0 g.) were heated under reflux in dry acetone (100 c.c.) in the presence of potassium carbonate (10·0 g.) for 4 hours. The suspension was filtered, treated with water (100 c.c.), and cooled to 0° for 18 hours. The bulky, colourless precipitate of *N-cyanomethyl-N′-methyl-N′-α-naphthylurea* (5·0 g.) was slowly formed, and crystallised from methanol in a voluminous mass of colourless felted needles, m. p. 198° (Found : C, 70·0; H, 5·0; N, 17·6. $C_{14}H_{13}ON_3$ requires C, 70·3; H, 5·4; N, 17·6%). This urea (3·0 g.) was heated under reflux for 2 hours with a solution of sodium ethoxide [from sodium (0·3 g.) in ethanol (30 c.c.)], and the solution evaporated to dryness *in vacuo*. The residue was suspended in water (30 c.c.), neutralised with acetic acid, and cooled to 0° for 3 hours. *5-Amino-2-N-methyl-α-naphthylamino-oxazole* (2·5 g.) was filtered off; it crystallised from methanol in sheaves of colourless spears, m. p. 191—192° (decomp.) (Found : N, 18·3. $C_{14}H_{13}ON_3$ requires 17·6%).

α-Methylamino-*n*-valeronitrile (11·3 g.) in ether (50 c.c.) was added to a solution of α-naphthyl *iso*cyanate (17·5 g.) in ether (50 c.c.) at 0° during 5 minutes. After cooling at 0° for 18 hours, the bulky precipitate of *N*-n-*cyano*-n-*butyl*-N-*methyl*-*N′*-α-*naphthylurea* (28·8 g., 100%) was filtered off and crystallised from benzene, forming large colourless rods, m. p. 151° (Found: C, 73·2; H, 6·8; N, 14·9. $C_{17}H_{19}ON_3$ requires C, 72·6; H, 6·8; N, 14·9%). Heating it under reflux for 2 hours with 10% ethanolic hydrogen chloride yielded 1-methyl-3-α-naphthyl-5-*n*-propylhydantoin,

colourless rectangular plates, m. p. 153° (from methanol) (Found: C, 72·1; H, 6·8; N, 10·0. Calc. for $C_{17}H_{16}O_2N_2$: C, 72·3; H, 6·4; N, 9·9%). The same urea (1·9 g.) was added to a solution of sodium ethoxide [from sodium (0·15 g.) in dry ethanol (25 c.c.)] and heated under reflux for 2 hours. Evaporation to dryness and acidification gave a precipitate of *5-amino-3-methyl-2-α-naphthylimino-4-n-propyloxazoline* (1·9 g., 100%), which crystallised from methanol in thick, massive rods, m. p. 198° (Found: N, 14·6. $C_{17}H_{19}ON_3$ requires N, 14·9%). It was much more stable to hydrolysis than any of the other compounds obtained in this series, being recovered substantially unchanged after 3 hours' refluxing with ethanolic hydrogen chloride; neither isomer nor dimer was obtained.

Compounds derived from α-Amino-nitriles and Phenyl iso*Cyanate.*—A solution of phenyl *iso*cyanate (11·6 g.) in ether (100 c.c.) was added during 5 minutes to a solution of ethyl aminocyanoacetate (12·5 g.) in ether (50 c.c.) at 0°. After 18 hours at 0°, the bulky precipitate of *N-cyanocarbethoxymethyl-N′-phenylurea* (21·5 g., 89%) was filtered off and crystallised from methanol, forming long, thin, colourless needles, m. p. 167—169° (Found: C, 57·9; H, 5·4; N, 16·9. $C_{12}H_{13}O_3N_3$ requires C, 58·3; H, 5·3; N, 17·0%). A solution of sodium ethoxide [from sodium (0·5 g.) in dry ethanol (50 c.c.)] was added to the above urea (5·0 g.). After 2 hours' heating under reflux the orange solution was evaporated to dryness *in vacuo*, and the crystalline residue treated with water (35 c.c.) and neutralised with acetic acid. The colourless precipitate of *ethyl 5-amino-2-anilino-oxazole-4-carboxylate* (4·1 g., 82%) was filtered off; crystallisation from aqueous methanol gave pale yellow cubes, m. p. 211—212° (Found: C, 58·3; H, 5·4; N, 17·0. $C_{12}H_{13}O_3N_3$ requires C, 58·3; H, 5·3; N, 17·0%).

α-Aminobenzyl cyanide (12·5 g.) in ether (100 c.c.) was cooled to 0°, and a solution of phenyl *iso*cyanate (11·5 g.) in ether (100 c.c.) added during 10 minutes. A voluminous white precipitate rapidly appeared, and the *N*-α-cyanobenzyl-*N′*-phenylurea (22·5 g., 94%) was collected after 72 hours at 0°. The urea crystallised from ethanol in colourless hairs, m. p. 155°. The same compound (12·5 g.) was heated with a solution of sodium ethoxide [from sodium (1·2 g.) in dry ethanol (200 c.c.)] under reflux for 1·5 hours. The yellow solution was evaporated to dryness *in vacuo*. The crystalline residue, suspended in ice-cold water (80 c.c.), was neutralised with acetic acid, and the resulting yellow precipitate collected after 12 hours at 0°. This solid was stirred with hot methanol (100 c.c.) and cooled to 0° for a further 12 hours. The colourless residue of 5-amino-2-anilino-4-phenyloxazole (1·7 g.) was collected; it crystallised from acetic acid as the *acetate* in colourless hexagonal plates, m. p. 217° (decomp.) (Found: C, 65·9; H, 5·4. $C_{17}H_{17}O_3N_3$ requires C, 65·6; H, 5·5%). Addition of cold water (100 c.c.) to the methanolic filtrates obtained above yielded a yellow precipitate of *2 : 4-di-imino-3 : 5-diphenyl-1-phenylcarbamyl-3-N′-phenylureidopyrrolidine hydrate* (9·5 g.), yellow prisms (from methanol–water), m. p. 94° (decomp.) (Found: C, 69·5; H, 5·6. $C_{30}H_{26}O_3N_6.H_2O$ requires C, 69·2; H, 5·4%).

α-Methylamino-*n*-valeronitrile (6·0 g.) in ether (20 c.c.) was cooled to 0°, and a solution of phenyl *iso*cyanate (6·5 g.) in ether (30 c.c.) added during 5 minutes. The colourless solution was kept at 0° for 24 hours, and a crystalline solid gradually deposited. This precipitate (4·7 g.) was filtered off, and addition of light petroleum (b. p. 40—60°) to the filtrate gave a further 5·0 g. of crystalline solid (total yield 84%). *N-α-Cyano-n-butyl-N-methyl-N′-phenylurea* crystallised from benzene containing 10% light petroleum (b. p. 40—60°) in long, thin, colourless rods, m. p. 77° (Found: N, 18·2. $C_{13}H_{17}ON_3$ requires N, 18·2%).

Compounds derived from α-Amino-nitriles and Methyl iso*Cyanate.*—A solution of methyl *iso*cyanate (3·0 g.) in ether (50 c.c.) was added to α-aminobenzyl cyanide (6·5 g.) in ether (50 c.c.) at 0° during 5 minutes. The crystalline precipitate of *N-α-cyanobenzyl-N′-methylurea* (8·3 g., 87%) was collected after 72 hours at 0° and recrystallised from methanol in long, thin, colourless needles, m. p. 166° (Found: C, 63·2; H, 5·9; N, 22·1. $C_{10}H_{11}ON_3$ requires C, 63·5; H, 5·8; N, 22·2%). This urea (6·7 g.) was heated with a solution of sodium ethoxide [from sodium (0·85 g.) in dry ethanol (50 c.c.)] under reflux for 1·5 hours. The dark solution was evaporated to dryness *in vacuo*, and the residue neutralised with aqueous acetic acid. After 13 hours at 0°, the yellow precipitate of *5-amino-2-methylamino-4-phenyloxazole* (3·2 g., 48%) was filtered off. Crystallisation was effected from acetic acid–light petroleum (b. p. 40—60°), giving small colourless needles, m. p. *ca.* 240° (decomp.) (Found: C, 64·3; H, 5·5. $C_{10}H_{11}ON_3$ requires C, 63·5; H, 5·8%). Heating the original urea with ethanolic hydrogen chloride gave, in the usual way, 3-methyl-5-phenylhydantoin which crystallised from aqueous methanol in square plates, m. p. 160°.

Ethyl aminocyanoacetate (10·5 g.) in ether (65 c.c.) was treated with an equivalent amount of methyl *iso*cyanate in ether (50 c.c.), added at 0° during 5 minutes. After cooling at 0° for 24 hours, the colourless precipitate of *N-cyanocarbethoxymethyl-N′-methylurea* (12·5 g., 78%) was

filtered off. It crystallised from methanol in long, thin, colourless needles, m. p. 164° (Found: C, 45·6; H, 5·9; N, 22·7. $C_7H_{11}O_3N_3$ requires C, 45·4; H, 5·9; N, 22·7%).

Compounds derived from α-Amino-nitriles and Sodium Cyanate.—α-Aminobenzyl cyanide (20·0 g.) was dissolved in 50% aqueous acetic acid and the solution cooled to 0°. Finely powdered sodium cyanate (10·0 g.) was added during 15 minutes with stirring. *N*-α-Cyanobenzylurea (26·5 g., 100%) was collected after 24 hours at 0°. After crystallisation from water, it had m. p. 177°. This urea (12·0 g.) was heated with a solution of sodium (1·6 g.) in dry ethanol (100 c.c.) under reflux for 1·5 hours. The solution became dark green and ammonia was steadily evolved. Evaporation to dryness *in vacuo* yielded a gum which was suspended in cold water and neutralised with acetic acid. After cooling to 0° for 24 hours, the yellow precipitate of 2 : 5-*diamino*-4-*phenyloxazole* (1·9 g., 16%) was filtered off and well washed with water (Found: C, 60·9; H, 4·9. $C_9H_9ON_3$ requires C, 61·7; H, 5·1%). It was insoluble in most organic solvents, but dissolved to a moderate extent in acetic acid, with partial decomposition.

Ethyl aminocyanoacetate (3·5 g.) was dissolved in 50% aqueous acetic acid (30 c.c.) at 0°. Finely powdered sodium cyanate (1·75 g.) was added during 8 minutes with stirring; a bulky white precipitate was soon formed. After cooling at 0° for 24 hours, N-*carbethoxycyanomethylurea* (3·3 g., 63%) was filtered off. It crystallised from methanol in long, thin, colourless needles, m. p. 166° (Found: C, 42·4; H, 5·5; N, 24·9. $C_6H_9O_3N_3$ requires C, 42·1; H, 5·3; N, 24·6%).

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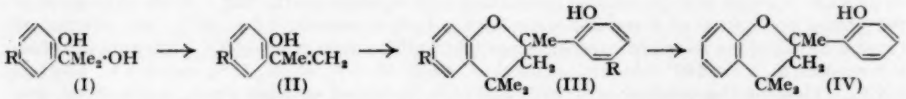
726. *Condensation Products of Phenols and Ketones. Part IX.* Dimerides of 4-Chloro- and 4-Bromo-2-isopropenylphenol.*

By WILSON BAKER, D. F. DOWNING, A. E. HEWITT-SYMONDS, and J. F. W. MCOMIE.

4-Chloro- and 4-bromo-2-*iso*propenylphenol (II; R = Cl and Br) have been prepared from methyl 5-chloro- and 5-bromo-salicylates by reaction with methylmagnesium iodide, and dehydration of the resulting alcohols (I; R = Cl and Br). The dimerides of these *o-iso*propenylphenols are shown to be 6 : 5′-dichloro- and 6 : 5′-dibromo-2′-hydroxy-2 : 4 : 4-trimethylflavan (III; R = Cl and Br respectively) by reduction to the known 2′-hydroxy-2 : 4 : 4-trimethylflavan (IV). The two halogenated flavans give crystalline adducts with dioxan and a number of organic bases.

IN Parts VI and VIII of this series (Baker, Curtis, and McOmie, *J.*, 1951, 76; 1952, 1774) it has been proved that the dimerides of certain *o-iso*propenylphenols, namely, 4-*iso*propenyl-*m*-cresol, 3-*iso*propenyl-*o*-cresol, and 3-*iso*propenyl-*p*-cresol, are all derived from 2′-hydroxy-2 : 4 : 4-trimethylflavan (IV) which is itself obtained by dimerisation of *o-iso*propenylphenol. It is shown in the present paper that 4-chloro- and 4-bromo-2-*iso*propenylphenol (II; R = Cl and Br respectively) dimerise similarly to 6 : 5′-dichloro- and 6 : 5′-dibromo-2′-hydroxy-2 : 4 : 4-trimethylflavan (III; R = Cl and Br), the structure of both these products being established by catalytic reduction to the known 2′-hydroxy-2 : 4 : 4-trimethylflavan (IV).



The *iso*propenyl compounds (II; R = Cl and Br) cannot be obtained by direct condensation of *p*-chloro- and *p*-bromo-phenol with acetone owing to the weak reactivity of the aromatic nuclei in these compounds. They were, therefore, prepared by treating the

* Part VIII, *J.*, 1952, 1774.

sodium salts of methyl 5-chloro- and 5-bromo-salicylate with methylmagnesium iodide; the resulting alcohols (I; R = Cl and Br) were then dehydrated by heat. Dimerisation to the flavans (III; R = Cl and Br) was brought about either by hydrogen chloride or by iodine.

Like the other flavans encountered in this work (except that obtained by dimerisation of 3-*iso*-propenyl-*o*-cresol) (see Part VII, Baker, Curtis, and Edwards, *J.*, 1951, 84; Part VIII, Baker, Curtis, and McOmie, *loc. cit.*), these substances form crystalline adducts (all 1 : 1) with dioxan and many organic bases. Of these flavans, that derived from *m*-cresol and acetone, namely 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan, forms the greatest number of crystalline complexes.

Experimental

M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford, and Mr. W. M. Eno, Bristol.

2-(5-Chloro-2-hydroxyphenyl)propan-2-ol (I; R = Cl).—5-Chlorosalicylic acid (Hirwe, Rana, and Gavankar, *Proc. Indian Acad. Sci.*, 1938, **8**, *A*, 208) gave the methyl ester, b. p. 120°/12 mm., m. p. 47°, in 93% yield (Varnholt, *J. pr. Chem.*, 1887, **36**, 21, gives m. p. 48°).

A mixture of finely divided sodium (2·3 g., 1 mol.) and toluene (40 c.c.) was vigorously stirred in an oil-bath at 100° whilst a solution of methyl 5-chloro-2-hydroxybenzoate (18·7 g., 1 mol.) was slowly added; a vigorous reaction set in with the separation of an orange sodium salt, and heating was continued for 1 hour. The cooled mixture was stirred whilst a solution of methylmagnesium iodide, prepared from magnesium (8·5 g.), methyl iodide (49·7 g.), and ether (60 c.c.), was slowly added, stirring was continued for 2 hours at room temperature, and the mixture was then boiled for 16 hours, cooled, poured into 50% aqueous acetic acid (130 c.c.), and extracted with ether (3 × 25 c.c.). The organic layer was washed with water and with 2N-sodium hydroxide (4 × 50 c.c.), and the alkaline layer after being shaken with ether was heated on the water-bath for 4 hours (to hydrolyse any methyl 5-chloro-2-hydroxybenzoate) and saturated with carbon dioxide. The precipitated solid was collected, washed, dried, and crystallised from light petroleum (b. p. 100—120°), giving 2-(*5-chloro-2-hydroxyphenyl*)*propan-2-ol* as thick, highly-refracting, hexagonal prisms (17·3 g.), m. p. 100·5° (Found: C, 57·8; H, 6·1; Cl, 18·9. $C_9H_{11}O_2Cl$ requires C, 57·9; H, 5·9; Cl, 19·0%).

6 : 5′-Dichloro-2′-hydroxy-2 : 4 : 4-trimethylflavan (III; R = Cl).—The alcohol (I; R = Cl) (12·2 g.) was dehydrated by heating it for ½ hour at 180°/560 mm., and then distilled, giving 4-chloro-2-*iso*propenylphenol (II; R = Cl) as an oil (8·1 g.), b. p. 75—80°/1 mm. This compound was then dimerised by cooling it in ice-salt and passing in a little hydrogen chloride; a strongly exothermic reaction occurred and the mixture became very viscous and crystallised after being kept at 40° for 48 hours. Crystallisation from light petroleum (b. p. 100—120°) gave *6 : 5′-dichloro-2′-hydroxy-2 : 4 : 4-trimethylflavan* as rhombic crystals (7·6 g.), m. p 110° (Found: C, 64·1; H, 5·4; Cl, 20·6. $C_{18}H_{18}O_2Cl_2$ requires C, 64·1; H, 5·3; Cl, 21·1%). The *acetyl* derivative, prepared by boiling the flavan (II; R = Cl) (3 g.) for 4 hours with acetic anhydride (20 c.c.) and anhydrous sodium acetate (3 g.) and shaking the mixture with water, separated from ethanol in prismatic needles (2·9 g.), m. p. 130° (Found: C, 63·4; H, 5·6; Cl, 18·3. $C_{20}H_{20}O_3Cl_2$ requires C, 63·3; H, 5·3; Cl, 18·7%).

Reduction of 6 : 5′-Dichloro-2′-hydroxy-2 : 4 : 4-trimethylflavan. Formation of 2′-Hydroxy-2 : 4 : 4-trimethylflavan (IV).—The dichloro-flavan (III; R = Cl) (1·0 g.) in methanol was reduced with hydrogen at 5 atmospheres pressure in presence of powdered anhydrous sodium acetate (0·5 g.) and 2½% palladium–charcoal (1·0 g.) for 5 hours. The filtered solution was poured into water, and the halogen-free solid (0·7 g., 88%), m. p. 96—97°, was crystallised from light petroleum (b. p. 60—80°), giving prisms, m. p. 97°, undepressed when mixed with authentic 2′-hydroxy-2 : 4 : 4-trimethylflavan of the same m. p. (Baker, Curtis, and McOmie, *J.*, 1952, 1780).

2-(5-Bromo-2-hydroxyphenyl)propan-2-ol (I; R = Br).—Methyl 5-bromosalicylate was prepared according to Peratoner (*Gazzetta*, 1886, **16**, 405), but chloroform was used as solvent in place of carbon disulphide. A solution of the ester (115 g., 0·5 mol.) in toluene (300 c.c) was slowly added to a vigorously stirred mixture of powdered sodium (11·5 g., 0·5 mol.) and toluene (200 c.c.) heated in an oil-bath at 100°, giving the light yellow sodium salt of the phenolic ester. The cooled mixture was then treated with methylmagnesium iodide (2 mols.) and the product worked up as in the case of the chloro-compound (above), giving 2-(*5-bromo-2-hydroxyphenyl*)*propan-2-ol* (71 g., 62%) as hexagonal prisms [from light petroleum (b. p. 100—120°)],

m. p. 88—89° (Found: C, 46·5; H, 5·0; Br, 34·6. $C_9H_{11}O_2Br$ requires C, 46·7; H, 4·9; Br, 34·6%).

4-*Bromo*-2-iso*propenylphenol* (II; R = Br).—The alcohol (I; R = Br) (71 g.) was heated for ½ hour at 180°/560 mm., and then distilled, giving **4-*bromo*-2-iso*propenylphenol*** as a viscous oil (45 g., 70%), b. p. 89—93°/2 mm. (Found: C, 50·4; H, 4·7; Br, 37·2. C_9H_9OBr requires C, 50·7; H, 4·2; Br, 37·6%).

6 : 5′-*Dibromo*-2′-*hydroxy*-2 : 4 : 4-*trimethylflavan* (III; R = Br).—4-Bromo-2-*iso*propenylphenol (II; R = Br) (4·6 g.) was dimerised (*a*) by addition of a crystal of iodine and warming on a water bath, the dimeride (III; R = Br) solidifying, after cooling, to a sticky mass, or (*b*) by passing in dry hydrogen chloride whilst cooling the whole in ice-salt [the dimeride separated after 5 minutes as in (*a*)]. In each case the product was first crystallised from light petroleum (b. p. 100—120°) (25 c.c.) and dioxan (1 c.c.) as the dioxan adduct, which was then heated (100°/1 mm.) till no further loss in weight occurred, and the free **6 : 5′-*dibromo*-2′-*hydroxy*-2 : 4 : 4-*trimethylflavan*** (III; R = Br) recrystallised from light petroleum (b. p. 100—120°) as rhombic crystals, m. p. 96° (Found: C, 50·6; H, 4·3; Br, 37·3. $C_{18}H_{18}O_2Br_2$ requires C, 50·6; H, 4·2; Br, 37·6%). The *acetyl* derivative, prepared by refluxing the flavan (III; R = Br) (0·5 g.) for 4 hours with acetic anhydride (2 c.c.) and pouring into water, separated from light petroleum (b. p. 100—120°) in prisms (0·48 g., 87%), m. p. 134° (Found: C, 51·0; H, 4·1; Br, 34·3. $C_{20}H_{20}O_3Br_2$ requires C, 50·3; H, 4·3; Br, 34·9%). The hydroxyflavan (III; R = Br) was insoluble in dilute aqueous sodium hydroxide, and did not give a colour with alcoholic ferric chloride. In concentrated sulphuric acid it gave a deep orange solution.

Reduction of* 6 : 5′-*Dibromo*-2′-*hydroxy*-2 : 4 : 4-*trimethylflavan (III; R = Br). ***Formation of* 2′-*Hydroxy*-2 : 4 : 4-*trimethylflavan*** (IV).—The flavan (III; R = Br) (0·4 g.) in ethanol (30 c.c.) was reduced with hydrogen at 5 atmospheres in the presence of powdered anhydrous sodium acetate (0·2 g.) and palladium black (0·05 g.) for 6 hours. The product, isolated as before, proved to be 2′-hydroxy-2 : 4 : 4-trimethylflavan (IV), m. p. and mixed m. p. 97° (yield of recrystallised material 0·2 g., 80%) (Found: C, 80·1; H, 7·3. Calc. for $C_{18}H_{20}O_2$: C, 80·4; H, 7·4%).

Adducts.—The *adducts* (all 1 : 1) obtained are listed in the Table. Neither compound forms adducts with the usual laboratory solvents or with quinoline, diethyl ketone, di*iso*propyl ketone, mesityl oxide, di*iso*butylamine, or β-picoline. The chloro-compound does not form adducts with di-*n*-propyl ketone, γ-picoline, or 2 : 4- or 2 : 6-lutidene; neither does the bromo-compound with di-*n*-butyl ether, di*iso*butyl ketone, di-*n*-propyl-, di-*n*-butyl-, or diethyl-amine, di*iso*propylamine, *cyclo*hexylamine, α-picoline, or 2-bromopyridine.

Addenda	M. p.*	Found, % C	H	N	Loss*	Required, % C	H	N	Loss
6 : 5′-*Dichloro*-2′-*hydroxy*-2 : 4 : 4-*trimethylflavan* (III; R = Cl).									
Dioxan	97°	62·4	6·3	—	20·3[a]	62·1	6·1	—	20·7
Diethylamine	95—96	—	—	3·0	17·8	—	—	3·3	17·8
Di-*n*-propylamine	87—88	65·3	7·5	3·5	23·0[b]	65·7	7·5	3·2	22·8
Di*iso*propylamine	97—98	—	—	2·8	22·8	—	—	3·2	22·8
Di-*n*-butylamine	66	—	—	2·9	27·3	—	—	3·0	27·7
*cyclo*Hexylamine	94	—	—	3·0	23·1	—	—	3·2	23·0
Morpholine	134	—	—	4·0	20·9	—	—	3·5	20·5
Piperidine	124	—	—	3·2	19·9	—	—	3·3	20·0
Pyridine	105	—	—	3·2	19·4	—	—	3·3	19·0
α-Picoline	86—87	—	—	3·2	22·0	—	—	3·3	21·8
6 : 5′-*Dibromo*-2′-*hydroxy*-2 : 4 : 4-*trimethylflavan* (III; R = Br).									
Tetrahydrofuran	125—126	53·0	5·5	—	14·3[c]	53·0	5·3	—	14·4
Dioxan	114	52·0	5·1	—	17·0[d]	51·5	5·1	—	17·1
Morpholine	146	—	—	2·7	16·7	—	—	2·7	16·9
Piperidine	141	—	—	2·6	16·2	—	—	2·7	16·3
Pyridine	120	—	—	2·9	15·8	—	—	3·1	15·6
3-Bromopyridine	93—94	—	—	2·0	26·6	—	—	2·3	27·0

* Dissociation. † At 100°/1 mm.

[a] Found: Cl, 16·6. Reqd.: Cl, 16·7%. [b] Found: Cl, 16·0. Reqd.: Cl, 16·2%. [c] Found: Br, 31·8. Reqd.: Br, 32·0%. [d] Found: Br, 32·3. Reqd.: Br, 31·3%.

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727. *Studies in Hydrogen-bond Formation. Part I. Detection of the Interaction of Phenols with Amido- and Azo-groups, etc., by Dielectric-constant Measurement.*

By C. H. Giles, T. J. Rose, and D. G. M. Vallance.

Hydrogen bonding between organic compounds is readily detected by dielectric-constant measurement of binary solutions in anhydrous solvents. Recent developments in apparatus design enable results to be obtained rapidly with simple equipment.

It is found that phenolic hydroxy-groups have a consistent tendency to bond with other similar groups or with nitrogen atoms in azo-, amino-, and secondary alkyl- and aryl-amido-groups, but not with a keto-group. Cross-linking of azo- and alkylamido-groups by dihydric phenols (resorcinol, quinol) has been detected. Two azo-groups appear to be cross-linked by only one dihydric phenol molecule, whereas two alkylamido-groups appear to be cross-linked by two dihydric phenol molecules in parallel. The amide group seems to react in the enol form and is bifunctional.

The hydrogen-bonding properties of organic molecules have received considerable attention in recent years, and much information is available on the formation of intra- and inter-molecular bonds by simple molecules, *e.g.*, *o*-nitrophenol, oxalic acid, and polymeric molecules in fibres (for summaries, see, *e.g.*, Pauling, "The Nature of the Chemical Bond," Ithaca, N.Y., Cornell Univ. Press, 2nd edn., 1944; Barrer, *J. Soc. Dyers Col.*, 1941, **57**, 264; Hunter, Price, and Martin, "The Hydrogen Bond," Royal Institute of Chemistry Lectures, Monographs, and Reports, 1950, No. 1). There is, however, little precise knowledge on hydrogen bonding between fibrous substrates and dyes or related materials, although it is believed that such bonding plays an important part in aiding the substantivity of dyes for most types of fibres (see, *e.g.*, Vickerstaff, "The Physical Chemistry of Dyeing," Edinburgh, Oliver and Boyd Ltd., 1950). It is proposed therefore to undertake a study of hydrogen bonding between typical groups found in fibres, dyes, and related reagents, suitable "model" compounds being used.*

It was decided first to examine the use of dielectric-constant measurements of solutions of such "model" compounds in anhydrous solvents, as a means of detecting intermolecular hydrogen bonding, because recent developments in circuit design enable a simple apparatus and technique to be employed. The present paper describes the apparatus and procedure and the results of some preliminary experiments with the method.

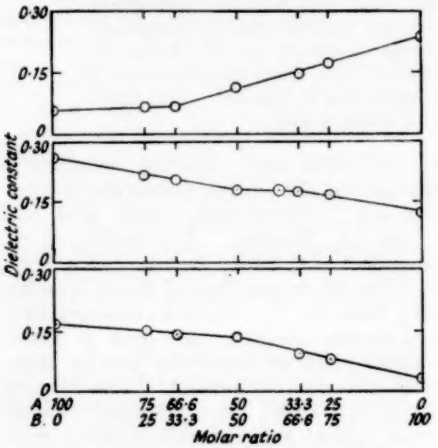
The dielectric constant of single organic compounds dissolved in inert, non-polar solvents is, in general, proportional to the concentration (cf., *e.g.*, Clark, "The Fine Structure of Matter," Chapman and Hall Ltd., London, 1938. Part II, Chap. X). In binary solutions of constant total molarity, but having varying proportions of the solutes, proportionality will hold only if no interaction occurs. If a donor compound, A=O, and an acceptor, H–B, interact, forming a complex, A=O → H–B, the dipole moment of the last will differ from that of either of the components, and a mixed solution will have a dielectric constant differing from the additive value. It can be shown (see Appendix) that the plot of the dielectric constant against molar proportion of solutes should show a change of slope at a point corresponding to the composition of the complex formed.

Previous Work.—Chrétien and Laurent (*Compt. rend.*, 1932, **195**, 792; 1934, **199**, 639), Laurent (*ibid.*, 1934, **199**, 582; 1935, **201**, 554), and Trinh (*ibid.*, 1948, **226**, 403) found distinct kinks in the curves of dielectric constant against relative molar concentration for a number of binary solutions of simple organic compounds in benzene, dioxan, and ether. They interpreted the results as a measure of the ease of salt formation between the

* Since this paper was submitted Flett (*J. Soc. Dyers Col.*, 1952, **68**, 59) has described a quantitative investigation, by infra-red spectrophotometry, of the heats and free energies of formation of hydrogen bonds between 21 pairs of simple organic compounds; none of these pairs is identical with any of those here described.

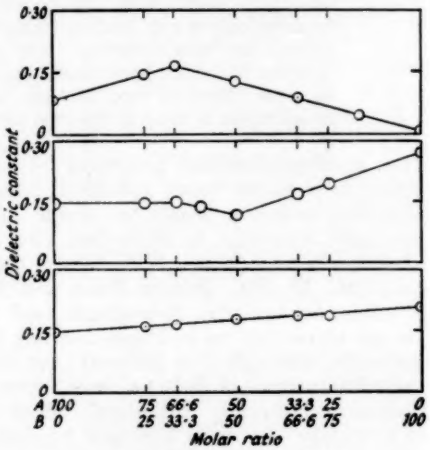
compounds examined and did not consider the possibility of hydrogen bonding. The mixtures they used included a number of mono-, di-, and tri-hydric phenols with nitriles, pyridine, and primary, secondary, and tertiary aliphatic and aromatic amines, and in most cases each phenolic group was found to unite with one nitrogen-containing group. A few exceptions were noted; *e.g.*, no interaction was detected between phenolic groups and dimethylaniline, *p*-phenylenediamine, or " aminophenol " (configuration unspecified). This was attributed to the reduced basicity of these three compounds. *o*-Nitrophenol was the only compound examined for interaction with azobenzene, with which it was found to associate in 2 : 1 ratio. No amides were examined. One hydrocarbon, triphenylmethane, was included; it formed a 1 : 1 complex with pyrrole.

FIG. 1. *Relation between dielectric constant* and component ratio in binary solutions.*



Top : A = Azobenzene. B = Aniline;
Middle : A = Aniline; B = Diethylamine.
Bottom : A = *o*-Nitrophenol; B = Diethylamine.

FIG. 2. *Relation between dielectric constant* and component ratio in binary solutions.*



Top : A = Phenol; B = Quinol.
Middle : A = Phenol; B = Azobenzene.
Bottom : A = Phenol; B = Benzophenone.

* The ordinates show increments of dielectric constant, on arbitrary base-lines, not absolute values.

Earp and Glasstone (*J.*, 1935, 1709, 1720) measured the dielectric constants of binary mixtures of acetone, dioxan, quinoline, and simple ethers, with chlorinated hydrocarbons, and calculated therefrom the mass-action constants of the complex-formation reactions and the amounts of the complexes present. They made some experiments with binary solutions of the reagents in *cyclo*hexane, but the deviations from additivity of the dielectric constants were too small to be of value in the calculations required. Intermolecular bonding was found to occur between oxygen and hydrogen attached to aliphatic carbon, especially if hydrogen is attached to a negative group, *e.g.*, a phenyl or nitrophenyl group.

Present Work.—The present work covers broadly an examination of the interaction of the phenolic hydroxy-group with the keto-group and with other phenolic hydroxy-groups; with nitrogen-containing groups, *e.g.*, the azo-, alkyl, and aryl-amide groups; with primary, secondary, and tertiary amino-groups; and with the nitro-group. The amides used were (*a*) *N*-*n*-butylpropionamide, chosen for its ease of preparation, suitable physical properties, and similarity to the repeat unit in both Nylon and protein fibre molecules, and (*b*) acetanilide, chosen because it contains the arylamide group, present in many dyes. In order further to study the properties of the two portions of the amide group separately, compounds containing individual keto- and secondary alkylamino-groups, respectively, were also examined. Two compounds likely to demonstrate the effect of an internal chelate link, *o*-nitrophenol and 2 : 3 : 4-trihydroxybenzophenone, were also included in the tests.

To carry out the examination of their bonding properties, the pairs of solutes for test are each separately dissolved in the same solvent at the same molar concentration. The required series of binary solutions is then readily prepared by mixing small volumes of the solutions, in the required ratios, measured from microburettes, and the mixtures are then stored in ground-glass stoppered test-tubes until required. The dielectric constants of the solutions are determined as described below and the values are plotted against the molar ratios. The curves are linear in almost every case, usually showing one distinct change of slope, and sometimes two. These changes always occur exactly at the simple molar ratios 1 : 1 or 1 : 2. In a few cases a single straight line is obtained, attributed to the absence of a complex, and in some cases the presence or absence of change of slope is uncertain. Some typical curves are shown in Figs. 1 and 2 and the conclusions drawn from the whole series of results are summarised in Table 1.

TABLE 1.

Solutes		Solution		
a	*b*	Solvent *	Total mol. concn.	Mol. ratio of complex (*a* : *b*) †
Acetanilide	Aniline	D	0·2	(1 : 1)
	Azobenzene	D	0·2	(1 : 1)
	Phenol	D	0·2	1 : 2
	Triethylamine	D	0·2	1 : 1
Azobenzene	Aniline	B	0·3	2 : 1
	Phenol	B	0·3	1 : 1; 1 : 2
	Catechol	E	0·3	1 : 1
	Resorcinol	E	0·3	2 : 1
	Quinol	E	0·15	2 : 1
N-*n*-Butylpropionamide	Phenol	B	0·3	1 : 2
	Catechol	E	0·3	(2 : 1)
	Resorcinol	E	0·3	1 : 1
	Quinol	E	0·15	1 : 1
	2 : 3 : 4-Trihydroxybenzophenone	E	0·3	2 : 1
	o-Nitrophenol	B	0·3	1 : 1
	p-Nitrophenol	E	0·3	2 : 1
	Azobenzene	B	0·3	1 : 1
Di*iso*butyl ketone	Aniline	B	0·3	‡
	Phenol	B	0·2	‡
	Catechol	E	0·3	(‡)
	Quinol	E	0·15	(‡)
	Azobenzene	B	0·2	‡
Diethylamine	Aniline	B	0·3	1 : 1; 2 : 1
	Phenol	B	0·2	1 : 1
	Catechol	E	0·3	1 : 1; 2 : 1
	Resorcinol	E	0·3	1 : 1; [1 : 2(?) (solid complex §)]
	Quinol	E	0·15	2 : 1; (1 : 1)
	o-Nitrophenol	B	0·3	1 : 1
	p-Nitrophenol	E	0·3	[2 : 1(?) (solid complex §§)]
	Azobenzene	B	0·2	1 : 1
Phenol	Benzophenone	B	0·25	‡
	Catechol	E	0·2	2 : 1
	Quinol	E	0·15	2 : 1
	Quinoline	B	0·2	1 : 1
	Triethylamine	B	0·2	1 : 1

* Solvents: B = benzene; D = dioxan; E = diethyl ether.
† Data in parentheses denote uncertain indications.
‡ No evidence of complex formation.
§ Colourless needles, m. p. 118°.
§§ Yellow needles, m. p. 88°.

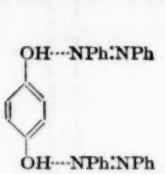
Crystalline complexes separated from the solutions of diethylamine with resorcinol (on storage) and with *p*-nitrophenol (when first mixed). These crystals were collected and analysed. Their empirical compositions did not exactly correspond to simple ratios of the components, though they approximated to the ratios shown in Table 1. This is

probably accounted for by selective removal of one of the components when the precipitate is washed with fresh solvent.

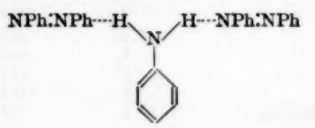
Discussion.—In the present work, only the *ratio* in which the solutes combine is strictly determined, but in most cases a consideration of the bonding tendencies of the individual groups, which is disclosed by the results as a whole, and, in some cases the use of scale-model molecules, enables the formula of the actual complex(es) formed to be given with some confidence.

There is a consistent tendency for each phenolic hydroxy-group to bond with one other similar group or with nitrogen atoms of the azo-, alkylamido-, and amino-groups. In the nitrophenols one oxygen of the nitro-group appears to form a bond with a hydrogen atom in the second solute; the internal chelate bond in the *o*-compound prevents the hydroxy-group from taking part in any such intermolecular bond, but in the *p*-isomer it can do so and as a result *p*-nitrophenol can cross-bond two alkylamido-groups. 2 : 3 : 4-Trihydroxybenzophenone reacts in the same ratio with the alkylamide group as does catechol, confirming the presence of a chelate linkage between the keto-group and the adjacent hydroxy-group.

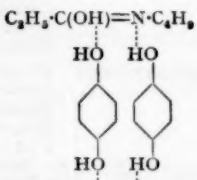
Two phenol molecules can unite simultaneously with the two nitrogen atoms of azobenzene.* The two active hydrogen atoms in quinol, resorcinol, and aniline must form cross-linkages with two azobenzene molecules † because this seems to be the most reasonable interpretation of the 2 : 1-ratio complexes detected [*e.g.*, as in (I) and (II)]. Examination of models shows that steric hindrance prevents two of the cross-linking molecules from combining in parallel with the azo-groups.



(I) With quinol.



(II) With aniline.



(III)

Catechol appears to be able to form complexes by means of either one or two of its hydroxy-groups. The 1 : 1-ratio complex observed with catechol–azobenzene solutions might therefore be interpreted either as evidence of a single hydrogen bond between one hydroxy-group and one azo-nitrogen atom, or of a complex in which each azo-nitrogen atom is attached to one of the hydroxy-groups of the catechol molecule. Although it can be shown, with scale models, that such a structure is possible with azobenzene in the normal *trans*-form, it seems less likely because it involves an eight-membered ring.

A study of models gives no evidence of steric hindrance to such double cross-bonding of alkylamido-groups and it does indeed appear to occur with *N*-*n*-butylpropionamide and resorcinol or with quinol, where complexes only of 1 : 1-ratio are detected. The only structural configuration which seems to satisfy this ratio is that shown in (III), it being borne in mind (*a*) that both hydroxy-groups in the aromatic compound appear to be equally reactive, and (*b*) that a polymer with a very long chain of cross-bonded groups (the only other possible configuration), would probably be insoluble.

There is no evidence that the phenolic hydroxy-group forms a stable bond ‡ with the keto-group in simple ketones, yet the ·CO·NH· group in both *N*-*n*-butylpropionamide and acetanilide appears to be bifunctional in forming hydrogen-bond complexes. This group may thus be reacting in the enol form, ·C(OH):N·, which could be considered bifunctional, because it is clear from Table 1 that both tertiary nitrogen atoms and hydroxy-groups can form bonds.

* Azobenzene itself thus differs from its *oo'*-dihydroxy-derivatives, in which only one hydroxy-group appears to be chelated with the azo-group (Schetty, *Textil-Rundschau*, 1950, **5**, 399).

† Similar cross-linking of azobenzene derivatives by quinol has been observed in monolayers on water (Giles and Neustädter, following paper).

‡ Some of the curves of solutions containing a ketone are not quite linear, though no kinks are present. This may indicate the formation of unstable complexes.

Experimental

(Microanalyses were by Drs. Weiler and Strauss, Oxford.)

N-n-*Butylpropionamide*.—Propionyl chloride (37 g.) was added dropwise to *n*-butylamine (58·4 g.) under a reflux condenser, in a flask cooled in a bath of ethanol and solid carbon dioxide. When addition was complete the mixture was heated to 80°, kept thereat for 15 minutes, and allowed to cool overnight. The liquor was then shaken with an equal volume of water, and the oily layer separated and retained. The aqueous layer was then shaken with ether and the ether extract added to the oil, which was then twice distilled, and the *amide* collected; yield: 45 c.c. of a colourless liquid, b. p. 236°/760 mm. (Found: C, 64·9; H, 11·6; N, 10·7. $C_7H_{15}ON$ requires C, 65·1; H, 11·6; N, 10·85%).

2 : 3 : 4-*Trihydroxybenzophenone* (Alizarin-yellow A, Colour Index, No. 1014).—Benzotrichloride (40 g.) was added slowly to pyrogallol (20 g.) in boiling 90% ethanol (40 g.), and the mixture poured into cold water; the product formed yellow needles, m. p. 139—140°, from water (Found: C, 67·7; H, 4·4. Calc. for $C_{13}H_{10}O_4$: C, 67·8; H, 4·35%).

Specially dried solvents of analytical reagent quality were used.

Measurement of Dielectric Constant.—Determination of dielectric constants depends on accurate capacitance measurement. Three procedures have been commonly used for this purpose: (*a*) the capacity bridge, (*b*) the heterodyne beat method, and (*c*) the resonance method.* Chrétien and Laurent used (*a*) (cf. Chrétien, *Compt. rend.*, 1931, **192**, 1385), and Earp and Glasstone used (*b*). In the present work, advantage has been taken of recent developments which enable the resonance method to be used with simple apparatus of high sensitivity. The instrument incorporates a tuned-anode, quartz crystal-controlled grid oscillator, based on the principle first employed for dielectric-constant measurement by Henriquez (Reilly and Rae, "Physico-Chemical Methods," Methuen and Co. Ltd., London, 3rd edn., 1940, Vol. II, pp. 509, 510). Energy is transferred between a tuned oscillatory circuit and the quartz crystal through the anode-grid capacitance of a triode valve, the condition of resonance being reached when the natural frequency of the tuned circuit approaches that of the quartz crystal and oscillation sets in. At the resonant frequency, the circuit offers maximum impedance to the direct current through it, and the change in anode current thus produced may be employed as a means of determining the oscillation point. A dielectric cell or condenser is placed in parallel with a calibrated tuning condenser in the anode oscillatory circuit, and the system tuned to resonance. Introduction into the cell of the dielectric medium to be tested, by altering the capacitance of the anode circuit, causes the circuit to go out of oscillation. The oscillation point is restored by re-tuning the variable condenser, the difference between the two readings of which gives a measure of the required dielectric constant.

A milliammeter was formerly employed for recording the change in anode current, but Alexander (*Electronics*, 1945, **18**, No. 4, 116) first employed an electron ray ("magic eye") tube to serve as a combined oscillator and tuning indicator of improved sensitivity.

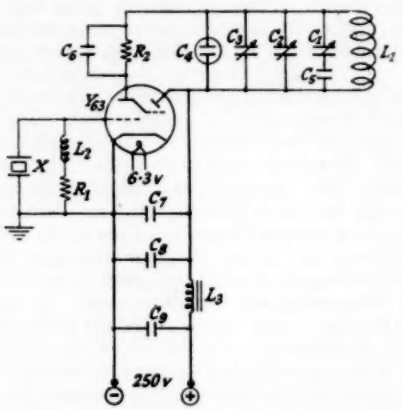
Design of Instrument.—The instrument (Fig. 3) used in the present work incorporates a Y 63 electron-ray ("magic eye") tuning indicator and is based on the circuits used by Alexander (*loc. cit.*), Bender (*J. Chem. Educ.*, 1946, **23**, 179), and Fischer (*Anal. Chem.*, 1947, **19**, 835). The triode portion of the indicator is used as the oscillator, and the target electrode as the resonance detector. The target, coated with fluorescent material, is positive with respect to the cathode. The resulting electron stream from cathode to target is influenced by a control electrode grid (internally connected with the triode anode), which, when it is made negative with respect to the target, deflects the electron stream, producing a shadow on the target, the normal "open eye." The angle of this shadow is reduced by making the control electrode more positive. In the non-oscillating position the anode current produces a large potential difference across the anode resistor R_2, which holds the anode and control electrode potentials at a low value with respect to the target; the "eye" is then open. When the anode and grid circuits are brought to resonance, the anode current decreases and therefore the potential difference across R_2 drops. Consequently, the potential of the control electrode with respect to the cathode, rises—it becomes less negative with respect to the target and the "eye" closes. The most convenient reference point for making measurements is the critical off-resonance capacity setting when the "eye" just flicks open or shut with increase or decrease of capacity, respectively.

* For a full discussion of the relative merits of (*a*), (*b*), and (*c*), see Smith, "Dielectric Constant and Molecular Structure," The Chemical Catalog Co. Inc., New York, 1931, Chap. 3.

The following are the values of the components used: C_1, 350 μμF; C_2, 12·5 μμF; C_3, 25 μμF; (C_4 is the dielectric cell); C_5, C_7, 0·01 μF; C_6, 0·001 μF; C_8, C_9, 2 μF; R_1, 1 megohm; R_2, 42,000 ohms; X, 4·55 Mc./s. quartz crystal; L_1, 11 turns of 20 S.W.G. enamelled copper wire close-wound on a 1-in. former; L_2, small R.F. choke; L_3, 7-Henry 50-mA choke. The condensers C_1 and C_2 are fitted with low-geared vernier dials. The dielectric cell (C_4) is constructed from a 12-μμF variable condenser, with silvered plates, by stripping all but one plate from the stator and all but two plates from the rotor. A brass stop is fitted so that the plates cannot be opened more than about half the maximum extent. The cell unit is connected to the main circuit by a short, screened cable. For use, the condenser plate assembly is submerged in about 20 c.c. of the liquid under test, contained in a small glass beaker.

Calibration of Instrument.—The instrument is switched on 15 minutes before use. It is first necessary to determine the values of the scale readings of the fine tuning condenser (C_2) against the main condenser (C_1). This procedure is repeated several times with a series of settings of C_1, the corresponding values of C_1 and C_2 being noted. In use, when the resonance position is reached, the reading of C_2, corrected to its value on C_1, is added to that of C_1.

FIG. 3.



The instrument is then calibrated, first with air and then with a series of pure liquids of known dielectric constant, as follows. With the plates of the measuring cell condenser open, in air, the anode and grid circuits are brought to resonance (the " eye " just flicks shut at this point), by tuning first with C_1 and then with C_2. The measuring cell plates are now closed, and C_1 and C_2 again adjusted to resonance. The difference between the two readings of C_1, each corrected by addition of the respective readings of C_2, gives the maximum capacitance increment in the measuring cell with air dielectric. The procedure is then repeated with the measuring cell filled with each liquid in turn. The dielectric constant of any liquid is given by the ratio of the maximum capacitance increments of the cell filled with that liquid and with air. (This method of measurement by using capacitance increments eliminates errors due to stray capacities between the cell, leads, and chassis.) The typical series of calibration readings in Table 2 shows that

TABLE 2. *Calibration of instrument.*

Dielectric	Air	Benzene	Ethyl ether	Chloro-form	Ethyl acetate	Quin-oline	Pyr-idine	Acetone
Dielectric constant	1·00	2·88	4·33	4·95	6·10	8·90	12·50	21·30
Max. capacitance increment of cell (dial reading)	96·04	92·64	86·84	85·80	81·77	74·20	62·22	32·00

the plot of dial readings (*i.e.*, values of C_1, corrected as described above) against dielectric constant is virtually linear over a wide range. In the present work, where only the relative values of dielectric constant of a series of liquids are required, a simpler procedure may be followed: readings are taken only with the condenser plates closed, and they may then be plotted directly against the molar ratios of the solutes in the solutions used.

The solutions of the two solutes to be examined were prepared and stored until required in ground-glass-stoppered tubes, then measured quickly in succession in the instrument at room temperature. After each solution had been measured, the plates were carefully washed with successive changes of pure dry ether and finally well dried in an air stream. The additional complication of thermostatic temperature control of the test liquid was considered unnecessary because the complete series of readings to detect complex formation between two solutes can be made in 30 minutes or less and any slight temperature variation between different series of experiments does not affect the position on the curves at which the changes of slope occur.

In an attempt to avoid the need for immersing the variable condenser plates in the test liquid, a method also used by Fischer (*loc. cit.*) and based on that proposed by Jensen and Parrack (*Ind. Eng. Chem. Anal.*, **1946**, **18**, 585) for conductiometric analysis, was examined. A circuit embodying the electron-ray indicator was employed and the oscillator was loaded by placing the test liquid in a glass tube, on which the coil of the anode oscillatory circuit was wound. The use of the method was not pursued, because with the available equipment the instrument proved less sensitive than the one described above and the calibration curve was not quite linear.

The results have been checked where necessary by examination of scale-model molecules.

Appendix

To demonstrate that the dielectric constant–concentration curve may be expected to show a break at the ratio of components corresponding to a complex, consider the special case of a binary solution, originally containing A molecules of a substance X and B molecules of a substance Y, in which z molecules of a complex Z, of formula XY have been formed. By the law of mass action $(A - z)(B - z)/z = 1/K$, where K is the equilibrium constant. Solving this for z, we have

$$z = \tfrac{1}{2}[(A + B + 1/K) \pm \sqrt{(A + B + 1/K)^2 - 4AB}]$$

Only the smaller root is a solution of this equation, since the larger one is greater than the larger of A and B and hence is impossible. It has a simple solution only if $1/K$ may be neglected in comparison with $A + B$, *i.e.*, if the compound is stable relative to X and Y, when $z = A$ or B, whichever is the smaller.

If we now measure any physical property of the binary solution (in this case the dielectric constant), which depends linearly upon the concentration of any of the three components of the solution considered separately, its value $\varepsilon_{obs.}$ is given by the expression

$$C\varepsilon_{obs.} = \varepsilon_X(A - z) + \varepsilon_Y(B - z) + \varepsilon_Z z$$

where $C = A + B$ and ε_X, ε_Y, ε_Z are respectively the physical constants (here, the dielectric constants) of the individual substances X and Y and the complex XY.

If the ratio $A : B$ is varied, $A + B$ remaining constant, then over the range $A < B$, we have $z = A$ and therefore

$$C\varepsilon_{obs.} = \varepsilon_Y(B - A) + \varepsilon_Z A = B(2\varepsilon_Y - \varepsilon_Z) - C\varepsilon_Y + C\varepsilon_Z$$

i.e., $\varepsilon_{obs.}$ varies linearly with B, the gradient being $(2\varepsilon_Y - \varepsilon_Z)/C$. Over the range $A > B$, $z = B$ and therefore $C\varepsilon_{obs.} = B(-2\varepsilon_X + \varepsilon_Z) + \varepsilon_X C$, $\varepsilon_{obs.}$ again varying linearly with B, and the gradient being $(-2\varepsilon_X + \varepsilon_Z)/C$. The two lines will intersect where $A = B = \frac{1}{2}C$, and at the intersection $\varepsilon_{obs.} = \frac{1}{2}\varepsilon_Z$.

The authors express their thanks to Professor P. D. Ritchie for his interest and advice, to Mr. J. C. Eaton and Dr. M. Gordon for their assistance with the Appendix, and to Mr. A. Ogilvie, for carrying out some of the dielectric-constant measurements.

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Royal Technical College, Glasgow, C.1. [*Received, December 27th*, 1951.]

728. *Researches on Monolayers. Part III.* The Effect of Mono- and Di-hydric Phenols on Monolayers of Certain Aromatic Compounds.*

By C. H. Giles and E. L. Neustädter.

Azo, hydroxy, and quinone groups in monolayers of aromatic compounds on water form a hydrogen bond with the hydroxy-group in monohydric phenols dissolved in the water phase. The increased water attraction thus imparted, *e.g.*, to the azo-group, may cause an expansion of the film by a change in the angle of tilt of the film molecule. Dihydric phenols in the water act in two ways: (*a*) If there are two suitably placed bonding groups in the monolayer molecule a 1 : 1-molecular complex may be formed, in which each of these groups is bonded with one hydroxy-group in the solute molecule; the two molecules probably stand parallel and side by side; a small increase in film area occurs and the compressibility may decrease. Quinol acts thus on (i) some hydroxyazo-compounds and (ii) benzoquinone and anthraquinone derivatives; with (ii) a quinhydrone-type compound appears to be formed. (*b*) If the solute hydroxy-groups are too far apart for (*a*) to occur, they may form cross-links between monolayer molecules, leading to a considerable increase in film area and compressibility.

A confirmation that the observed effects are caused by hydrogen bonding, and not merely by penetration of the film by bulky solute molecules, is afforded by the absence of significant changes in film area or compressibility when pyridine is used as solute below films of compounds with which it cannot form a hydrogen bond.

The orientation of surface-active azo-compounds in monolayers on water, and on dilute acid and alkali, has been described in Parts I and II (*J.*, 1952, 918, 1864). Many of the most important classes of dye contain the azo-group, which, besides acting as a chromophoric centre in the molecule, is believed to be partly responsible for their adsorption to fibres, by reason of hydrogen-bond formation with suitable groups, *e.g.*, hydroxy-groups in cellulose and the peptide link in protein fibres (see, *e.g.*, Vickerstaff, "The Physical Chemistry of Dyeing," Oliver and Boyd, London and Edinburgh, 1950).

The present paper describes preliminary investigations to determine if such hydrogen-bond formation, both with azo-compounds and other classes of dye, is detectable by experiments on monolayers. Some of the hydroxyazo-compounds already described, and other surface-active bodies containing groups commonly met in dyes and/or fibres, *e.g.*, quinone and imino-groups, have been used, and their bonding properties with hydroxy-compounds, in particular with phenols, have been studied.

Alexander (*Proc. Roy. Soc.*, 1941, *A*, **179**, 470, 486) has examined intra- and inter-molecular hydrogen bonding in monolayers of aliphatic amides and has in one case tentatively suggested a link between two such monolayer molecules through a water molecule. Schulman and Rideal (*ibid.*, 1937, *B*, **122**, 29, 46) have also studied the effect of polyhydric phenols upon protein mono-layers. No systematic study of bonding to fibre substrates by using the monolayer technique, however, appears to have been reported.

For the present research, compounds (VII)—(XIV) (see Table 1) have been prepared, and their film-forming properties on water examined. The action of certain solutes introduced into the aqueous phase has also been studied, by using monolayers of compounds (VII)—(XIV) and of typical azo-compounds (I)—(VI) selected from those described in Parts I and II. The exact choice of structure in compounds (VII)—(XIV) was dictated partly by the need to incorporate the desired groups and partly by the availability of the starting materials.

As solutes in the aqueous phase, phenol itself and also various dihydric phenols and ethylene glycol were used; pyridine was included, to study the effect of a water-soluble molecule which is of similar size to phenol, but has no hydrogen atom free to form an intermolecular bond.

The results are summarised in Tables 1 and 2, and typical curves are shown in Figs. 1—3.

* Part II, *J.*, 1952, 1864.

TABLE 1. *Molecular areas and compressibilities of monolayers on aqueous solutions of phenols, etc.*

No.	Compound	θ *	Molecular area (Å²) at zero compression and (in parentheses) compressibility † on: H_2O	0·1N-aqueous solutions of §: *a*	*b*	*c*	*d*	*e*	*f*	*g*
	Azo-compounds without hydroxy-groups.									
I	*p*-Dodecylazobenzene	—	No film formed	No film formed	—	—	—	—	—	—
II	4-Hexadecyloxyazobenzene	70° ‡	,,	37 (0·23)	—	—	—	—	—	—
III	4′-Hexadecyloxybis(phenylazo)benzene	90	38 (0·13)	(0·36) 48	—	—	—	37 (0·23)	—	—
	o-Hydroxyazo-compound.		(0·16)	(0·42)	(0·42)	(1·23)	(1·33)	(0·12)	(0·29)	(0·38)
IV	*p*-Dodecylaniline → *β*-naphthol	60	42·5	102	113	152	198	44	80	110
	p-Hydroxyazo-compound.		(0·09)	(0·40)	(0·19)	(0·65)	(1·23)	(0·29)	(0·12)	(0·30)
V	Hexadecyl *p*-aminobenzoate → *o*-cresol	50	44	51	52	122	175	42	48	50
	oo′-Dihydroxyazo-compound.		(0·09)		(0·14)					
VI	*o*-Aminophenol → *p*-hexadecylphenol	80	47	—	51	—	—	—	—	—
VII	*N*-Methylstearamide	—	(0·03) 21	(0·05) 23	(0·08) 29	(0·36) 44	—	—	—	—
VIII	*N*-*n*-Butylstearamide	—	No film formed	—	—	—	—	—	—	No film formed
IX	2-*p*′-Dodecylphenyl-*p*-benzoquinone	80	26 (0·02)	27·5 (0·04)	27 (0)	54 (0·31)	—	—	25 (0)	—
X	2-*p*′-Dodecylphenyl-*p*-quinol	—	(Oxidises)	—	—	—	—	—	—	—
XI	3-*p*-Dodecylanilinomethyl-2-naphthol	90	(0·19) 31	—	(0·18) 31	—	—	—	—	—
XII	1-Stearamidoanthraquinone	60	48 (0·09)	—	(0·05) 55	(0·60) 69	—	—	(0·11) 53	—
XIII	2- ,,	40	42 (0·09)	—	53(0·05)	—	—	—	50 (0·14)	—
XIV	2-Anthraquinonyl stearate	90	33 (0·03)	—	34 (0)	39 (0·16)	—	—	34 (0·01)	—

* θ = Probable angle of orientation on water of longest aromatic axis.
† Expressed as the tangent of the angle to the vertical of the upper portion of the π–A curve (Figs. 1—3).
‡ On phenol solution.
§ *a* = Phenol; *b* = *p*-quinol; *c* = 1 : 5-dihydroxynaphthalene; *d* = sodium 1 : 2 : 4 : 5 : 6 : 8-hexahydroxyanthraquinone-3 : 7-disulphonate; *e* = pyridine; *f* = ethylene glycol; *g* = catechol.

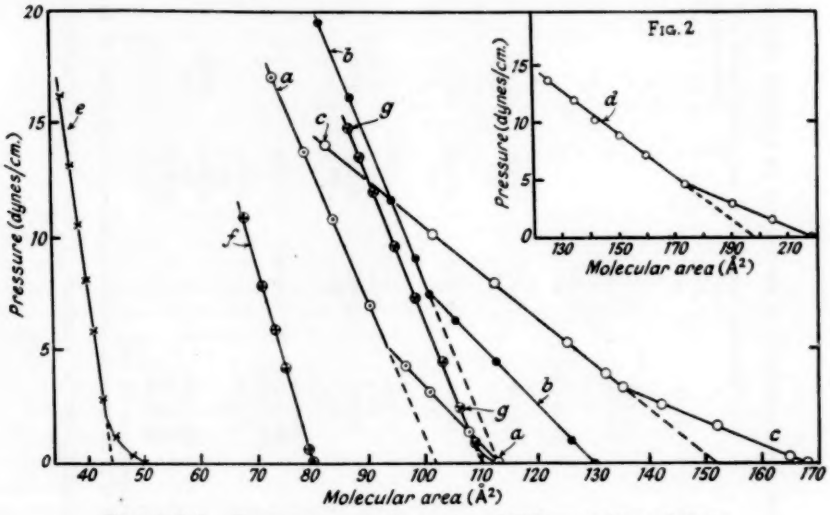
Table 1 gives the data on which most of the conclusions are based; Table 2 shows the areas at which surface pressure is first observed and at which the upper (linear) part of the π–A curve commences.

Monolayers on Water.—Compound (VIII) does not form films. This is undoubtedly owing to a steric effect, the water-attracting "head" group being prevented from penetrating the water surface sufficiently, by reason of the configuration of the hydrocarbon groups on either side (cf. Adam, "The Physics and Chemistry of Surfaces," Oxford Univ. Press, 3rd edn., 1941, Chap. II). (I) and (II) do not form films because the azo-group has insufficient water attraction (see Part I).

Compounds (VII) and (IX)—(XIV) all form stable condensed films. The molecular areas are consistent with orientation of the aromatic nuclei in a vertical plane, but the axis may in some cases be tilted parallel to this plane at an angle determined by the nature and position of the attached groups.

The closest packing of the benzoquinone compound (IX) is achieved when the molecule

FIG. 1. FIG. 2.



FIGS. 1 & 2. *Force–area curves for compound* (IV) *on various substrates.*

(*a*) *Phenol.* (*e*) *Pyridine.*
(*b*) *Quinol.* (*f*) *Ethylene glycol.*
(*c*) 1 : 5-*Dihydroxynaphthalene.* (*g*) *Catechol.*
(*d*) *Sodium* 1 : 2 : 4 : 5 : 6 : 8-*hexahydroxyanthraquinone*-3 : 7-*disulphonate.*

TABLE 2. *Areas* (Å²) *at* (i) *commencement of development of surface pressure and at* (ii) *lowest point of upper* π–A *curve.*

Compound	H_2O (i)	H_2O (ii)	*a* (i)	*a* (ii)	*b* (i)	*b* (ii)	*c* (i)	*c* (ii)	*d* (i)	*d* (ii)	*e* (i)	*e* (ii)	*f* (i)	*f* (ii)	*g* (i)	*g* (ii)
	Substrate : *															
II	—	—	57	32	—	—	—	—	—	—	—	—	—	—	—	—
III	48	35	60	42	—	—	—	—	—	—	48	35	—	—	—	—
IV	45	42	102	94 †	130	100 †	168	135 †	219	174	50	43	80	80	112	107 †
V	45	44	67	44 †	60	47 †	134	98 †	180	172	47	39	52	47	56	48 †
VI	53	46	—	—	52	48	—	—	—	—	—	—	—	—	—	—
VII	23	21	29	22	32	26	53	37 †	—	—	—	—	—	—	—	—
IX	26	26	32	27	31	27	60	51	—	—	—	—	29	25	—	—
XI	31	31	—	—	31	31	—	—	—	—	—	—	—	—	—	—
XII	54	48	—	—	58	55	80	62	—	—	—	—	56	52	—	—
XIII	44	41	—	—	57	53	—	—	—	—	—	—	53	49	—	—
XIV	37	33	—	—	42	34	53	36	—	—	—	—	39	34 †	—	—

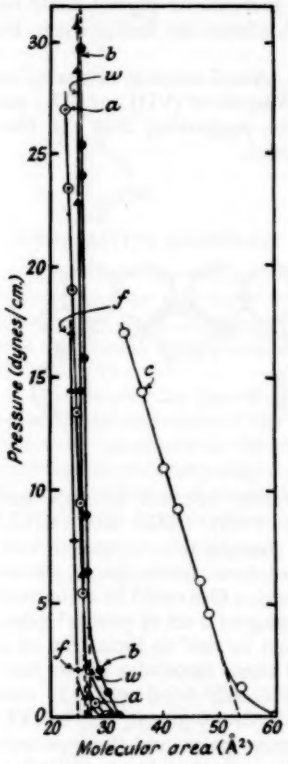
* For key, see table 1.
† Denotes linearity of the lower portion of the π–A curve.

is tilted as shown in Fig. 4. This corresponds to a repeat distance, perpendicular to the plane of the aromatic rings, of 3·5—4 Å, which appears rather too small to accommodate a bridging water molecule, in the manner suggested for the azo-compounds (see Part I).

The quinol derivative (X) is oxidised too readily in the film for reliable measurements to be made. A quinhydrone is probably formed, because when wiped away the film is seen to be dark green.

Compound (XIV) appears to stand with its anthraquinone nucleus vertical, some of the molecules perhaps being forced up a little above the level of the remainder to assist

FIG. 3. *Force–area curves for compound (IX) on various substrates.*



(*a*) *Phenol.* (*f*) *Ethylene glycol.*
(*b*) *Quinol.* (*c*) 1 : 5-*Dihydroxynaphthalene.*
(*w*) *Water.*

FIG. 4. *Probable orientation of* (IX) *on water* ($\theta = 80°$).

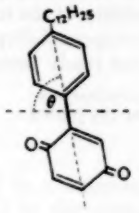


FIG. 5. *Probable orientation of* (XIV) *on water* ($\theta = 90°$).

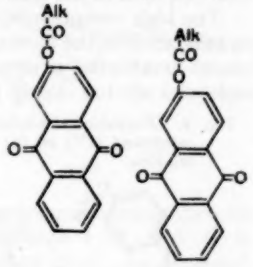
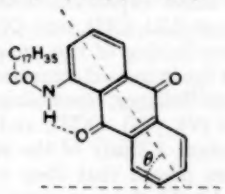
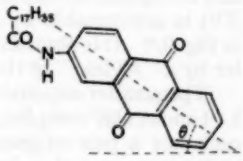


FIG. 6. (XII) ($\theta = 60°$).



(α)

FIG. 7. (XIII) ($\theta = 40°$)



(β)

Probable orientation of 1- *and* 2-*stearamidoanthraquinone* (XII *and* XIII, *respectively*).

close packing of the quinone groups (Fig. 5). The repeat distance perpendicular to the rings is thus about 4·5 Å. This is greater than the value for (IX). The reason may be that greater separation is necessary to accommodate the $-O-\overset{|}{C}=O$ group, which cannot lie in quite the same plane as the rings.

The water-attraction of the amide group in (XII) and (XIII) causes a pronounced tilt (Figs. 6, 7) and the molecules are less closely packed than are those of (XIV).

Monolayers on Phenol Solution.—The effect of a hydrogen bond between the phenolic hydroxyl group and an azo-nitrogen atom, combined with the water attraction of the ether oxygen atom, is sufficient to enable a stable film of (II) to be formed on phenol solution. The bond between phenol and the azo-group alone is insufficient to promote film formation, for (I) is not film-forming either on water or on phenol solution.

(VIII) does not form a film on phenol solutions, confirming that steric factors are preventing anchorage to the water surface; otherwise, phenol might be expected to attract the ·CO·NH· group sufficiently to cause monolayer formation.

Phenol causes a large increase in the apparent area of the *o*-hydroxyazo-compound (IV), but only a small increase in that of the *p*-hydroxyazo-compound (V). The *p*-compound is already tilted considerably on water, and any further tilt which might follow a greater solubilising action on the hydroxy, azo, or ester group would have little effect on the apparent molecular area. The observed increase can, in fact, be accounted for by an additional tilt of some 10°. In the case of the *o*-hydroxyazo-compound (IV) the additional attraction of the azo-group for the aqueous phase, imparted by the presence of phenol, must cause a considerable change in tilt. The observed area increase on phenol could be accounted for by a change in tilt of some 90° (Fig. 8), which allows the azo-group to be more exposed to the water phase.

The high compressibility values of the azo-compounds on phenol solution seems to be an indication of the increased solubility of the molecules; monolayers of (VII) and (IX) are almost unaffected in area and compressibility by this solute, suggesting that the film molecules are too closely packed for ready penetration by phenol.

FIG. 8. *Probable orientation of an* o*-hydroxyazo-compound* (IV) *on* (a) *water and* (b) *phenol solution.*

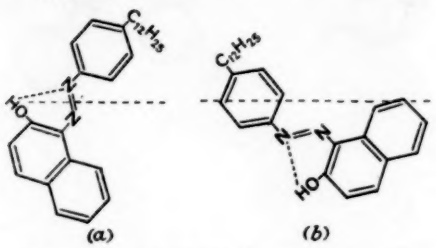
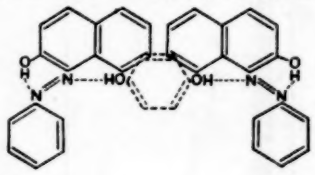


FIG. 9. *Cross-linking of* (IV) *by quinol.*



Monolayers on Quinol Solution.—Quinol causes considerable increase in area and compressibility of (IV); a small expansion with (V), (VI), (VII), (XII), and (XIII), and no significant expansion of (IX), (XI), and (XIV). The considerable expansion with (IV) is attributable to a cross-linking of the azo-groups in adjacent molecules as shown in Fig. 9.* It is obvious that the increased compressibility of such a film could be accounted for by a " folding " of the cross-linkages, resembling the collapsing of a set of parallel rules.

The smaller expansion of (V), (VI), (XII), and (XIII) must be due to formation of a 1 : 1-molecular complex, because a study of the structure of these molecules shows that each has a pair of groups so placed that they can simultaneously bond with the two hydroxy-groups of quinol. In (V) the azo-group and the *p*-hydroxy-group, and in (VI) one hydroxy-group and one azo-nitrogen atom,† are the effective pairs, and the quinones can similarly react to form quinhydrone-type complexes. The quinol molecule in such a complex must lie flat against the quinone or azo-molecule; thus the film expansion is much less than when cross-bonding occurs (Figs. 10, 11). The compressibility of the quinones (XII, XIII) is slightly reduced by this complex formation, as might be expected, but that of the azo-compounds (V, VI) is somewhat increased and in these, therefore, cross-linkage must occur to a small extent.

Penetration of the film of the benzoquinone compound (IX) by quinol appears to be limited ‡ and no penetration appears to occur with (XIV), presumably because of the tight packing of the film molecules.

* The $C_{(3)}$-hydroxy-group of the naphthalene nucleus is probably chelated with one azo-nitrogen atom, as shown, leaving one nitrogen atom free to form the intermolecular bond. For clarity, the N····H bonds between quinol and the azo-groups are not shown to scale. The $C_{12}H_{25}$ groups are omitted from Fig. 9.

† Schetty (*Textil-Rundschau*, 1950, **5**, 399) has shown that in *oo'*-dihydroxyazo-compounds only one hydroxy-group is chelated with an azo-nitrogen atom.

‡ That some reaction occurs is shown by the deep green colour of this film when it is wiped off the quinol solution.

Monolayers on Solutions of Dihydroxy-compounds of Large Molecular Size.—1 : 5-Dihydroxynaphthalene produces a considerable increase in both area and compressibility of films of (IV), (V), (VII), (IX), and (XII). This must be due to cross-linking of two molecules of the film by the dihydroxy-molecule (Fig. 12), but the two hydroxy-groups in the latter are only very slightly further apart * than are those in quinol, so that the much greater increases in the film areas produced by 1 : 5-dihydroxynaphthalene are an indication that the plane of the aromatic rings in these cross-linking compounds lies parallel to the water surface, they may, indeed, float on the surface.

FIG. 10. 1 : 1-*Complex formation of* (*a*) (V) *and* (*b*) (VI) *with quinol.*

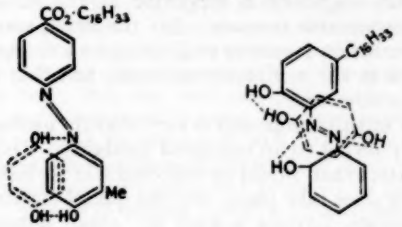
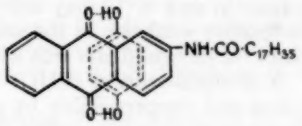


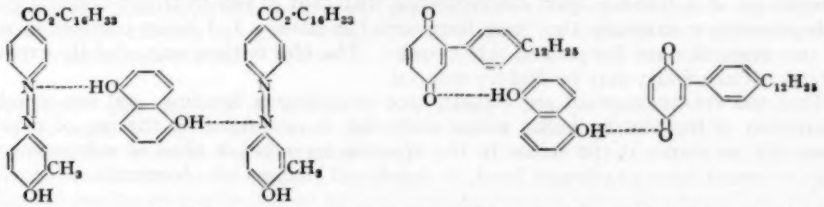
FIG. 11. 1 : 1-*Complex formation of* (XIII) *with quinol.*



A greater expansion should be produced by a water-soluble compound having phenolic hydroxy-groups still more widely separated in the molecule. Sodium 1 : 2 : 4 : 5 : 6 : 8-hexahydroxyanthraquinone-3 : 7-disulphonate was found suitable for trial. As expected, this compound does produce a striking increase in area and compressibility of films of (IV) and (V).

It is noteworthy that the film of (XIV) is so tightly packed and the van der Waals forces between the molecules of the large underwater " head " so great that very few dihydroxy-molecules can penetrate the monolayer. Quinol is without effect and even 1 : 5-dihydroxynaphthalene produces only a small increase in area and compressibility, which may be due to a limited degree of cross-linking. A less likely cause of the small area increase might be 1 : 1-complex formation across the ester group and the most remote quinone group.

FIG. 12. *Cross-linking by* 1 : 5-*dihydroxynaphthalene.*



Monolayers on Pyridine.—The molecule of pyridine is of roughly the same size and shape as that of phenol or quinol, but it has no hydrogen atom free to form a bond. It was thought, therefore, that a study of its action in the aqueous phase below the film might confirm the belief that the effects produced by the hydroxy-compounds are indeed due to hydrogen bonding and not merely to a penetration of the film by unbonded solute molecules. If hydrogen bonding alone is responsible for the increases in the apparent molecular area and compressibility of, *e.g.*, (IV), produced by quinol, then films of this substance on pyridine solution should have the same characteristics as they do on water, because, if the hydroxy-group in (IV) is chelated with one of the nitrogen atoms in the azo-group, there is no group capable of forming a hydrogen bond with pyridine. The data in Table 1 (col. *e*) show that pyridine has, in fact, no significant effect on the area of films of (IV) or of (III). There is a small increase in compressibility.

* The distances, centre-to-centre, between the pairs of oxygen atoms are about 6 Å and 6·5 Å in quinol and 1 : 5-dihydroxynaphthalene, respectively.

When present below films of a compound having a free hydroxy-group (*e.g.*, V), pyridine increases the compressibility, but slightly decreases the molecular area. These effects can be attributed to the effect of bonding between the solute and the hydroxy-group in the film molecule. This would cause an increased solubility of the latter, and perhaps some change in its orientation.

Monolayers on Ethylene Glycol.—The molecular areas and compressibility data suggest that this compound is unable to penetrate the films of (IX) and (XIV), but that it probably causes an increased tilt of the molecules of the azo-compounds (IV, V) and the stearamido-anthraquinones (XII, XIII) by increasing the solubility of hydroxy and/or ester groups.

Monolayers on Catechol Solution.—The large increase in compressibility of (IV) and (V) suggests that cross-linking is taking place; this suggestion is supported by the value of the molecular area of (IV), which shows a considerable increase; but the much smaller increase in area of (V) may indicate that re-orientation occurs as well, owing to a change in the relative solubility of the substituent groups in the monolayer molecule, and that this masks the increased film area which would otherwise occur.

N-*Methylstearamide* (VII).—The monolayer of this compound is very slightly increased in area and compressibility by phenol, possibly owing to an enhanced solubility. Quinol has a very much smaller effect on these parameters than would be expected if cross-linkage occurred, and it may be that hydrogen bonding does take place, but the quinol molecules lie parallel with the lines of stearamide molecules, forming a kind of "chain linkage," rather than at right angles to them, as they would do in cross-linking. The larger molecule of 1 : 5-dihydroxynaphthalene causes a much greater increase in area and compressibility. This may be due to some cross-linking at right angles to the lines of stearamide molecules.

Conclusion.—The general conclusion is that hydroxy-groups in a solute beneath the monolayer form hydrogen bonds with azo, quinone, amide, etc., groups in the monolayer molecules, provided that these are not too tightly packed to allow penetration of the solute. If the solute is a monohydric compound, the effect is to increase the attraction of the film-forming substance for water, often with a change in the orientation of the molecules in the layer and an expansion of the film.

Solutes having two hydroxy-groups may use both of them in forming bonds with suitable groups in the monolayer molecule. This they may do in either of two ways: (*a*) they may form cross-links between two monolayer molecules, thus considerably expanding the film and increasing its compressibility, or, (*b*) if two hydroxy-groups in the solute molecule are at a distance apart corresponding with that of two hydrogen-bonding groups in the monolayer molecule, they may form with the latter a 1 : 1-molar complex in which the two molecules are flat-packed side-by-side. The film is then only slightly expanded and its compressibility may be slightly reduced.

That the effects recorded are actually due to hydrogen bonding, and not merely to penetration of the film by bulky solute molecules, is confirmed by the use of pyridine. When this substance is the solute in the aqueous layer below films of substances with which it cannot form a hydrogen bond, no significant changes are observed.

Experimental

The film balance, the general technique used, and the preparation of compounds (I)—(VI) have been described in Parts I and II. The scale deflection of the film balance was 1·0 cm. per dyne.

In the present work, for the aqueous phase, distilled water alone or 0·1N-solutions therein of the water-soluble phenols, etc., in pure form were used. Sodium 1 : 2 : 4 : 5 : 6 : 8-hexahydroxyanthraquinone-3 : 7-disulphonate was an exception; it was a commercial sample of the dye alizarine-cyanine WRS (Bayer) (Colour Index No. 1063); it was readily soluble in water to a dark maroon solution [Found: purity (by $TiCl_3$ titration), 62%, 6 atoms of hydrogen being assumed to be required per mol. of dye]. Paper chromatography showed only traces of coloured impurities; the main impurity was probably sodium chloride.

The conclusions have been checked by the use of Stuart-type molecular models (see Appendix).

N-*Methylstearamide* (VII).—Methylamine hydrochloride (10 g.) was suspended in chloroform (50 c.c.) and to it was added, during 5 minutes, stearoyl chloride (44·5 g.) in chloroform (50 c.c.) at room temperature, with stirring and cooling. *N*-Methylmorpholine (30·7 g.), dissolved in

chloroform (50 c.c.), was then added during 30 minutes. After a further hour, the solution was filtered and washed with dilute hydrochloric acid, sodium carbonate, and water successively. After being dried (Na_2SO_4), the chloroform was distilled off, and the residue recrystallised from alcohol; it formed colourless prisms, m. p. 91° (Found: C, 76·7; H, 12·8; N, 4·4. Calc. for $C_{19}H_{39}ON$: C, 76·8; H, 13·1; N, 4·7%).

N-n-*Butylstearamide* (VIII).—Stearoyl chloride (30 g.) was added slowly with cooling (in cold water) to *n*-butylamine (5·9 g.). A solid mass resulted; this was washed with dilute hydrochloric acid to remove any amine and recrystallised from alcohol, followed by ether, giving white needles of the *amide*, m. p. 70° (Found: C, 78·2; H, 13·5; N, 4·3. $C_{21}H_{43}ON$ requires C, 77·9; H, 13·3; N, 4·1%).

2-p′-*Dodecylphenyl*-p-*benzoquinone* (IX).—This was prepared by Kvalnes's method (*J. Amer. Chem. Soc.*, 1934, **56**, 2478), from *p*-dodecylaniline (26·2 g., 1 mol.) which was diazotised as described in Part I. The *quinone* formed pale yellow prisms, m. p. 76°, from acetic acid (Found: C, 81·6; H, 9·2. $C_{24}H_{38}O_2$ requires C, 81·8; H, 9·1%).

2-p′-*Dodecylphenyl*-p-*quinol* (X).—The quinone (IX) was reduced by boiling it under reflux for 2 hours with zinc dust and acetic acid. The red solution became yellow and the *quinol* was then precipitated in water; it formed prisms (from acetic acid), m. p. 80° (Found: C, 81·6; H, 9·4. $C_{24}H_{34}O_2$ requires C, 81·4; H, 9·6%).

3-p-*Dodecylanilinomethyl*-2-*naphthol* (XI).—This was obtained by the reduction of the corresponding keto-compound, prepared by dissolving 3-hydroxy-2-naphthoic acid (5 g.) in a small volume of toluene to which *p*-dodecylaniline (7 g.), dissolved in toluene, and phosphorus trichloride (5 g.) were added. The mixture was heated under reflux for several hours, and the product, m. p. 160°, recrystallised from benzene and then reduced. A solution of lithium aluminium hydride (1 g.) in 30 c.c. of ether was placed in a 3-necked flask fitted with a stirrer, and a solution of the amide (3·3 g.) in ether was added gradually, with stirring, to produce gentle refluxing. On completion of the reaction, water was added cautiously and the mixture was finally poured into ice and water acidified with sulphuric acid. The aqueous layer was extracted with ether, the extract evaporated, and the *product* recrystallised from benzene; it formed prisms, m. p. 114° (Found: C, 83·7; H, 9·2. $C_{29}H_{39}ON$ requires C, 83·5; H, 9·35%).

1- *and* 2-*Stearamidoanthraquinone* (XII, XIII).—1- or 2-Aminoanthraquinone (22·3 g.) and stearoyl chloride (30 g.) were dissolved in nitrobenzene and heated under reflux for 5 hours (Newton and F. Bayer and Co., B.P. 3055/1909). On cooling the solution crystals separated; recrystallisation from pyridine gave yellow needles, m. p. 120° and 182°, respectively (Found: (XIII) C, 78·3; H, 8·7; N, 3·1. (XIV) C, 78·3; H, 9·1; N, 3·0. $C_{32}H_{43}O_3N$ requires C, 78·4; H, 9·0; N, 2·9%).

2-*Anthraquinonyl Stearate* (XIV).—A solution of stearoyl chloride (30 g.) in nitrobenzene was added to a hot solution of 2-hydroxyanthraquinone (22·4 g.) in nitrobenzene. Heating was continued for 30 minutes at 180°. The *product* separated on cooling; and formed prisms, m. p. 85° from ethanol (Found: C, 78·6; H, 8·6. $C_{32}H_{42}O_4$ requires C, 78·4; H, 8·6%).

Appendix.—Determination of Orientation Angles from Molecular Models. Two Stuart-type models of each molecule are placed flat on squared paper, and oriented at different angles to a line representing the water surface, until a position is found satisfying the following requirements:

The two models are just in contact and are each at the same level, and oriented at the same angle, relative to the surface line; and the water-attracting groups are slightly beneath the surface line. It is found in nearly all cases that there is one such position where the repeat distance is a minimum; the corresponding orientation angle is given in the Tables in this paper and in Parts I and II.

We are indebted to Professor P. D. Ritchie for his interest and encouragement, and to Mr. A. Pajackowski for assistance with some of the syntheses. We also thank the Directors of Imperial Chemical Industries Limited, Dyestuffs Division, for financial assistance to one of us (E. L. N.), and for the supply of several intermediates.

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729. *The Salting-out of Non-electrolytes. Part I. The Effect of Ionic Size, Ionic Charge, and Temperature.*

By T. J. Morrison.

An empirical equation containing three constants is suggested to express the solubilities of gases at various temperatures. Lithium chloride, and probably also barium chloride, lanthanum chloride, and hydrochloric acid, cause a salting-out effect which is uniformly less than that expected when the ionic size is compared with that of sodium chloride. Potassium chloride behaves normally. Potassium iodide causes specific decreases in salting-out as compared with sodium chloride and this effect increases with increasing molecular size. The salting-out of gases generally diminishes with rise in temperature. The partial molar heat capacity of the gas is affected, the greatest diminution being for lithium chloride and the least for potassium iodide. It is therefore suggested that the effect of ions on the structure of the solvent plays an important part in the salting-out effect.

Nearly all recent work on salting-out has been carried out with weak or non-electrolytes of somewhat complex types. Data on simpler non-polar molecules are presented here in an attempt to extend the experimental work in this field. It is generally agreed that the effect varies in an approximately linear manner with concentration, and more attention has therefore been paid to variation in type of electrolyte and temperature.

(i) *Gas Solubilities.*—It has been found that the solubilities of the gases used can be expressed accurately by empirical equations of the type:

$$\log_{10} s_0 = -A + B/T + C \log_{10} T$$

where s_0 is conveniently expressed as the absorption coefficient at 1 atm. per 1000 g. of water. Values of the constants are given in Table 1, and the validity of the equations is shown by plotting the deviations between experimental and calculated values of $\log_{10} s_0$ ($\Delta \log s_0$) in Fig. 1 and 2. Deviations between recorded values and those obtained by the present method are also shown. Results for oxygen and carbon dioxide are included for comparison with fairly modern determinations, although no salting-out experiments have yet been done on these gases. Deviations generally correspond to not more than $\pm 0{\cdot}5\%$ in solubility so far as the present method is concerned, but some of the older results are almost certainly in error, especially for ethane and nitrogen, where the discrepancy may reach 8% in s_0. Certain modifications (see following paper, p. 3819) in the experimental procedure previously described (*J.*, 1948, 2033) lead to results which are in some cases slightly higher than recorded values, but for oxygen and carbon dioxide the results are in excellent agreement with more recent measurements by different methods. The method appears to be more satisfactory than Ostwald's technique at higher temperatures.

Table 1.

Gas	A	B	C	A/C	B/C	Gas	A	B	C	A/C	B/C
H_2	36·250	1847	12·65	2·866	146·0	C_2H_4	69·697	3900	23·70	2·941	164·6
CH_4	77·067	4090	26·20	2·941	156·1	N_2	81·328	4160	27·70	2·936	150·2
C_2H_6	87·699	4730	29·67	2·956	159·4	O_2	69·053	3685	23·50	2·938	156·8
C_3H_8	99·629	5445	33·50	2·974	162·6	CO_2	51·375	3280	17·48	2·939	187·6
n-C_4H_{10}	109·258	5995	36·60	2·985	163·8						

The theoretical significance of the large values of C, which is directly related to the partial molar heat capacity of the gas, has been indicated by Frank and Evans (*J. Chem. Phys.*, 1945, **13**, 478). There is an evident parallelism between the three constants, shown by the ratios given in Table 1, and although the values of A and B are determined to a large extent by the accuracy with which C can be estimated, the ratios A/C and B/C are

little affected by moderate variations in C. The error in C may be about 1·5 units, corresponding to about ± 3 cals. in $\bar{c}_p$. The constancy of C within these limits for each gas suggests that the temperature dependence of $\bar{c}_p$ is small over the range used. It has been found that the type of equation given applies well to most of the data recorded for aqueous solubilities even over much greater temperature ranges, *e.g.*, to the results on the

FIG. 1.

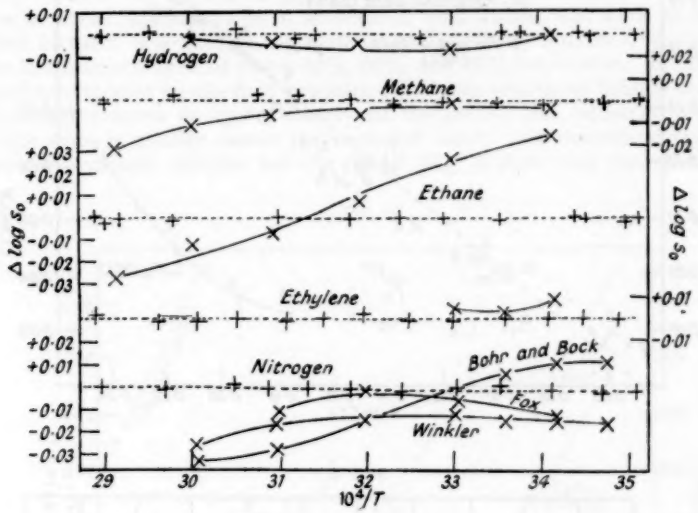
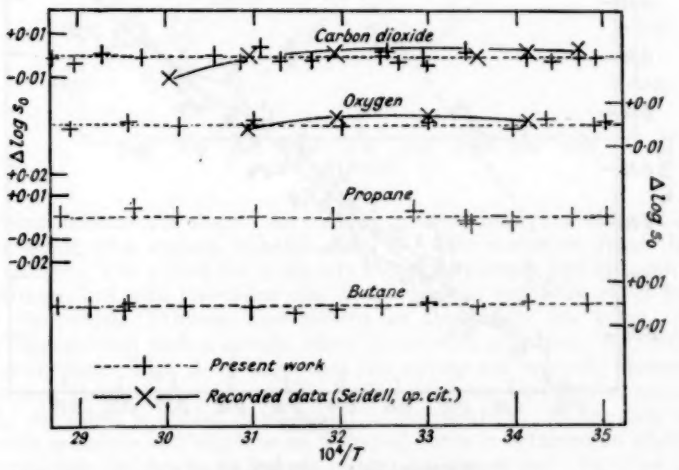


FIG. 2.



solubilities of hydrogen, helium, and nitrogen at high pressures (Seidell, " Solubilities of Inorganic and Organic Substances," van Nostrand, N.Y.)

(ii) *Salting-out.*—(a) *Ionic size and charge.* Since it does not appear to be practicable to calculate theoretical values of $k = (\log_{10} s_0/s)/c$, comparative methods are used. Values of k_X for a given salt are plotted against k_{NaCl} at temperatures corresponding to values of $1/T$ of (1) 0·0035, (2) 0·0033, (3) 0·0031, and (4) 0·0029. All measurements refer to 1000 g. of water. Theories of the salting-out effect generally agree that k should be proportional

FIG. 3.

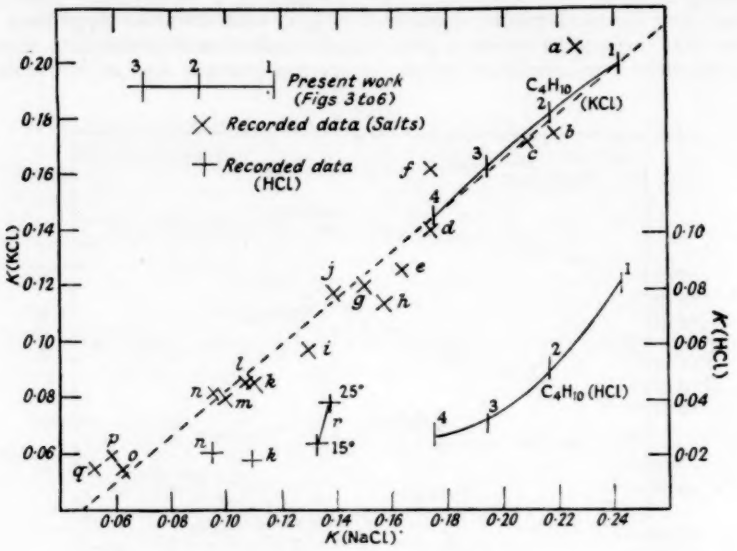
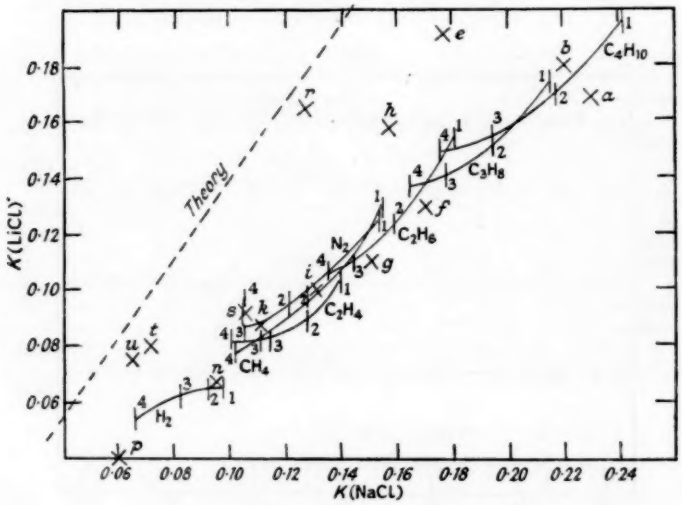


FIG. 4.



Recorded data. (Seidell, *op. cit.*)

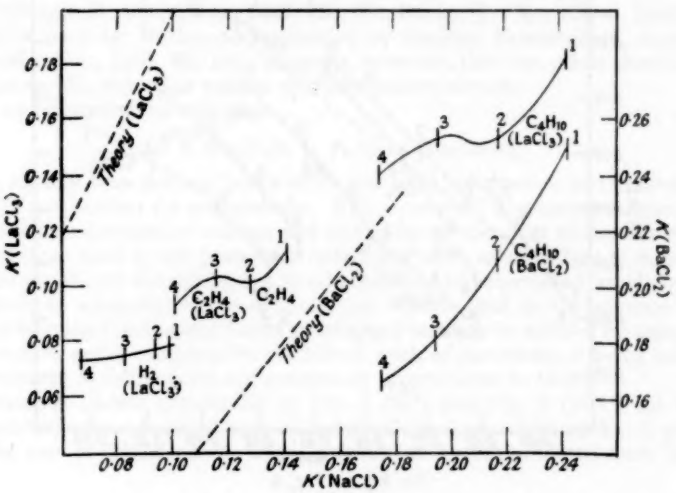
a, Ether.
b, Phenol.
c, Benzoic acid (85°).
d, ,, (60°).
e, ,, (25°).
f, Ethyl acetate.
g, Aniline (25°).
h, Quinol.
i, Phenylthiourea.
j, Diacetone alcohol.
k, N_2O.
l, Acetone.
m, C_2H_2.
n, H_2.
o, H_2S.
p, A.
q, He.
r, O_2.
s, CO_2.
t, Quinone.
u, Acetic acid.

to the quantity $\Sigma ce^2/a$, although the values to be taken for ionic radii may be in doubt. By using crystallographic values (Pauling) the following theoretical ratios of k_X/k_{NaCl} are found:

LiCl	KCl	KI	$\frac{1}{2}BaCl_2$	$\frac{1}{3}LaCl_3$
1·38	0·82	0·76	1·28	1·98

The effect of potassium chloride (Fig. 3), as judged from published data and the present results on *n*-butane, appears to be in accordance with theory, and work on this salt was not carried further. For lithium, lanthanum, and barium chlorides (Figs. 4 and 5) the slopes are less than expected by about 40%, 60%, and 25% respectively, and the reduction is a *general* one, at least for the first two salts. Previous results for lithium chloride in the cases of non-electrolytes lie approximately on the general line, although for weak electrolytes the ratio is usually nearer the expected value. No theoretical ratio has been calculated for hydrogen chloride, but the results (Fig. 3) show that the effect is probably

FIG. 5.



a large general reduction in slope. An entirely different behaviour is found on comparing potassium iodide with sodium chloride (Fig. 6). The variations from the theoretical slope are *specific*. The salting out is slightly high for hydrogen and nitrogen in potassium iodide solutions, but with increasing size in the paraffin series the effect becomes much less than theoretical. Ethylene also showns an abnormally low value. Study of the literature suggests that such a specific effect occurs with other ions, *e.g.*, NO_3'.

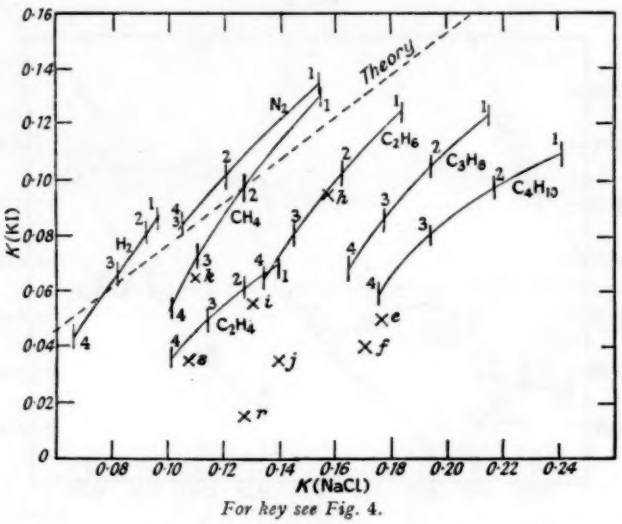
(b) *Temperature.* Figs. 3—6 show that the salting-out generally decreases with rise in temperature, though in some cases (N_2–LiCl) a minimum may be reached, and in others (H_2–$LaCl_3$) the effect is almost independent of temperature. In the case of lanthanum chloride with *n*-butane and ethylene an S-shaped curve is obtained on plotting k against $1/T$, but this may be due to hydrolysis of the lanthanum ion. In other cases plots of this type are not generally quite linear, showing that $\bar{c}_p$ for the gas may be affected, and making comparisons of heats and entropies of solution or even the values of k itself at fixed temperatures of doubtful value. Because of the difficulty of estimating the values of C in the empirical equations with sufficient accuracy, the values of the changes in $\bar{c}_p$ produced by salts presented in Table 2 can only be regarded as very approximate, but the general trend of the results is believed to be significant. The results for lanthanum chloride indicate that in the low-temperature region the changes in $\bar{c}_p$ are negative and

TABLE 2. $\Delta\bar{c}_p$ (*cals./deg./g.-mol.*).

Salt	Gas						
	N_2	CH_4	C_2H_6	C_3H_8	C_4H_{10}	C_2H_4	H_2
LiCl	−23	−15	−14	−12	−12	−8	+5
NaCl	−19	−10	− 7	− 4	− 4	0	+6
KI	−16	− 8	− 5	− 2	+ 6	+3	+8

probably greater than for lithium chloride. Barium chloride and hydrogen chloride appear to have effects of the same order as for lithium chloride, and potassium chloride has approximately the same effect as sodium chloride. The fact that lithium chloride decreases $\bar{c}_p$ to a greater extent than does sodium chloride, while potassium iodide has a more positive effect than sodium chloride is the main reason for the general curvature evident in Figs. 4 and 6 in the lines for individual gases. In Fig. 4 (LiCl–NaCl) the slope generally diminishes with rise in temperature, whereas in Fig. 6 (KI–NaCl) the slope

FIG. 6.



For key see Fig. 4.

increases. These slopes give, of course, the ratio of the change in heat of solution produced by salt X to that produced by sodium chloride.

If the views of Frank and Evans (*loc. cit.*) on the origin of the large values of $\bar{c}_p$ for gases in water are correct, the considerable changes produced by salts, which may amount to 40% of the original value, suggest that modification of the solvent structure in the vicinity of the non-electrolyte molecules cannot be neglected in theories of salting-out, at least at the concentrations used. It is noteworthy that ions which, according to Frank and Evans, tend to bring about a "structure building" effect, *e.g.*, Li^+ and La^{3+}, reduce $\bar{c}_p$ to a considerably greater extent than "structure-breaking" ions, *e.g.*, I^-; in fact, it is only potassium iodide which is found to increase $\bar{c}_p$ above the value for water, apart from the case of hydrogen. At the same time any attempt to deal with the problem on the basis of a hypothetical temperature change will be unsuccessful, since $\bar{c}_p$ for the gases in water certainly does not vary with temperature to nearly the same extent as on addition of salts. The considerable difference between the behaviour of nitrogen and of hydrogen supports the suggestion of Frank and Evans, based on rather meagre data, that the nature of the "ice-bergs" responsible for the large thermal characteristics of gases in water, may vary for different gases.

TECHNICAL COLLEGE, BRIGHTON.

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730. *The Salting-out of Non-electrolytes. Part II.* The Effect of Variation in Non-electrolyte.*

By T. J. Morrison and F. Billett.

The salting-out of a number of gases and aromatic liquids has been compared with the requirements of theory, molecular volume and total polarisation being used as variable characteristics of the solute molecules. For gases, part of the salting-out appears to be independent of these variables, and the remainder varies in an approximately linear manner for a group of gases. Ethylene and the aromatic hydrocarbons do not lie on the same line. The invariant portions of the effect give values for the primary hydration of the salts which are of the correct order of magnitude, but place the salts in the inverse order to that generally accepted.

Current theories of the salting-out effect require a knowledge of the effect of the solute molecule on the dielectric constant of the solvent to predict the approximate magnitude of the effect (Bebye, *Z. phys. Chem.*, 1927, **130**, 56; Butler, *J. Phys. Chem.*, 1929, **33**, 1015). The deduction used by Butler, and extended by Bockris, Bowler-Reed, and Kitchener (*Trans. Faraday Soc.*, 1951, **47**, 184), suggests, however, that the effect should depend to a large extent on the molecular volume of a non-polar molecule.

Butler's equation may be written:

$$k = Kv_c(p_b/v_b - p_c/v_c) = Kv_c(\Delta p/v)$$

where k has already been defined, and p and v are total polarisation and molecular volume of a solute (c) and solvent (b) respectively; K is a constant containing temperature, ionic radii, and dielectric constant of solvent and should be independent of the solute.

The substances used in the present investigation have small values of p_c/v_c compared with those for water, and the salting-out should therefore be determined largely by v_c. Some difficulty arises in assigning values of molecular volume, but in the absence of data on partial molar volumes it is thought that a satisfactory test can be applied by using molecular volumes measured under comparative conditions, such as parachors, it being assumed that the actual volumes in solution are approximately proportional to these.

The results are shown graphically in Fig. 1 (25°) and Fig. 2 (71·7°) for three salts. Values of $v_c(\Delta p/v)$ were calculated from recorded values of parachors and total polarisations except in the case of ethylbenzene, where a value for p_c was obtained from the additive

Table 1.

NaCl				LiCl			
At 25°		At 71·7°		At 25°		At 71·7°	
I	H_2O	I	H_2O	I	H_2O	I	H_2O
0·07	8	0·055	7	0·05	6	0·035	4

nature of total polarisation. No essential difference in the nature of the curves is found if values for k are plotted against the actual parachors. For the saturated hydrocarbons with sodium and lithium chlorides there appears to be a reasonably linear relation between salting-out and the polarisation factor, and the results for hydrogen and nitrogen fall fairly near this line. If the relation is a linear one, however, an appreciable amount of salting-out appears to be independent of the properties of the solute gas. It was considered at first that this might be ascribed to primary hydration of the salt. The approximate intercepts (I) and the number of molecules of water corresponding to this salting-out are given in Table I. The order of magnitude of the calculated hydration is in agreement with the values collected by Bockris (*Quart. Reviews*, 1949, **3**, 173), although the effect for sodium chloride is somewhat greater than for lithium chloride.

The results for potassium iodide do not appear to be in agreement with the above view.

* Part I, preceding paper.

If the lines are regarded as approximately linear, the intercept at 25° (excluding H_2) indicates a higher primary hydration than for lithium chloride, which is unlikely. The results at higher temperature, however, show a distinct curvature for the paraffin series and the curve might pass through the origin. The solution of the problem of the precise nature of the variation of k with molecular volume seems to require in the first place data on non-polar substances which are salted-out to an even smaller extent than those used in the present work, and it is hoped that work on the inert gases will provide this. The points

FIG. 1.

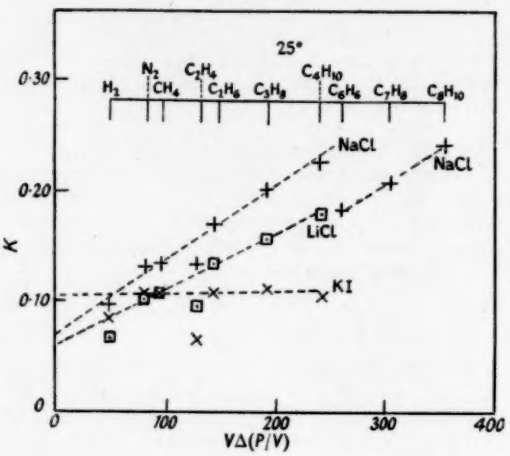


FIG. 2.

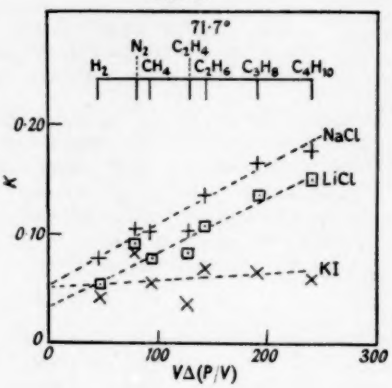
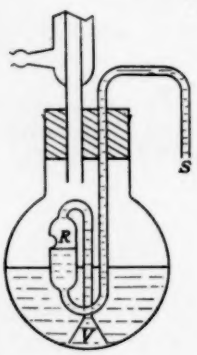
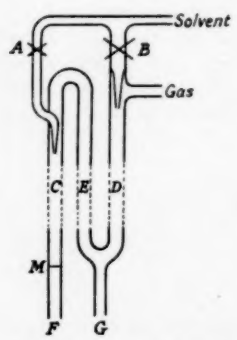


FIG. 3.



S, Siphon to solubility apparatus.
R, Constant-level reservoir
V, Vapour pump.

FIG. 4.



for the aromatic series, although approximately linear, involve too great an extrapolation, but it is noteworthy that, the parachor being used as a measure of molecular volume, they fall on a different line from the aliphatic series. Ethylene also lies consistently off the aliphatic line. It therefore appears that Butler's simple treatment of the effect does not include a sufficient number of variables to predict the behaviour of even relatively simple molecules. The treatment by Bockris and his co-workers, which may be regarded as introducing a salting-in term in Butler's equation, suggests that any salting-in occurring in these systems will be greatest for C_4H_{10}–KI, the combination of the largest ions and the most polarisable molecule, and least for H_2–LiCl. It is therefore possible that the anomalous behaviour of potassium iodide is due, in part at least, to the dispersion effect used in the above theory. The structural effect mentioned in Part I may also be in part responsible for the rather complex behaviour described.

Experimental (Parts I and II)

(i) *Gas Solubilities.*—An improved method of preparing solvents has been devised in place of that described (*J.*, 1948, 2033). This is based on the vapour-pump principle (Fig. 3) and ensures constant level, freedom from bumping, and more rapid removal of dissolved gases. Considerable use has also been made of the modification mentioned in the previous paper in which the gas measuring tube is separated from the absorption tube. In Fig. 4, *C*, *E*, and *D* are respectively a spiral with absorption tube, a gas burette, and a levelling tube (which also has a short spiral to ensure saturation). Readings are taken with liquid in *C* at the mark *M*. *F* leads to the graduated cylinder and *G* is used when filling with gas. This type of apparatus has the great advantage that gases with such diverse solubilities as nitrogen and carbon dioxide can be studied. The possibility of error due to the thin film of liquid in the absorption tube of the previous apparatus is also removed, and the absorption tube can more easily be filled with solvent at the end of a run so that the tube is always kept wet, an essential point if the apparatus is to be used for many determinations. The substitution of rubber tubing and clips for greased taps at *A* and *B* also contributes to the useful life of a tube.

The paraffin hydrocarbons were prepared from Grignard reagents. A sample of *n*-butane, stated to be over 99% pure, was kindly supplied by the Anglo-Iranian Oil Company, and gave the same results as gas prepared from Grignard reagents. Ethylene was prepared from ethanol and phosphoric acid, hydrogen from pure zinc and hydrochloric acid (giving the same results as a sample of electrolytic hydrogen). Nitrogen from a cylinder and from ammonium nitrite gave the same results within experimental error. Carbon dioxide was prepared from marble and hydrochloric acid, the usual precautions being taken with regard to freedom from air. Oxygen from a cylinder gave the same results as that from potassium permanganate (Table 2).

Table 2. *Solubilities of gases (in c.c. at N.T.P.) per* 1000 *g. of water at a total gas pressure of* 1 *atm.* (s_0).

Temp.	s_0	Temp.	s_0	Temp.	s_0	Temp.	s_0	Temp.	s_0
Hydrogen		Methane		Ethane		Propane		*n*-Butane	
12·3°	19·23	11·9°	39·90	12·3°	53·46	12·3°	50·70	10·9°	43·85
16·1	18·71	14·7	37·41	12·6	52·60	15·5	45·39	14·1	38·28
17·3	18·54	20·5	32·96	16·4	47·53	21·5	37·07	20·0	30·83
23·0	17·86	25·2	30·06	17·6	46·13	22·8	35·65	25·0	25·88
25·0	17·70	35·0	25·35	24·6	38·55	25·5	32·58	30·1	22·18
33·2	16·98	41·0	23·82	30·5	33·73	26·0	32·21	35·0	19·41
45·0	16·37	46·8	22·44	32·5	32·36	31·5	28·25	40·1	16·98
47·3	16·29	51·8	21·38	35·3	30·83	40·3	22·86	45·0	15·14
54·4	16·18	62·3	19·86	40·9	28·25	49·0	19·50	49·9	13·77
60·3	16·07	71·5	19·10	49·1	25·23	59·0	16·94	58·0	11·99
65·5	16·14	75·2	18·84	62·4	21·88	64·5	16·03	65·4	10·86
71·7	16·14			69·5	20·80	74·1	14·55	66·0	10·72
				71·4	20·46			70·8	10·16
				72·4	20·46			76·1	9·71

Ethylene		Nitrogen		Oxygen		Carbon dioxide			
13·8°	140·9	12·5°	18·37	12·7°	36·39	13·3°	1059	42·5°	502·0
17·1	128·8	15·5	17·22	13·5	35·56	14·9	1010	46·4	465·0
20·5	118·0	20·3	15·89	17·3	32·58	17·6	927	48·4	455·0
21·1	115·1	25·5	14·76	21·5	30·13	19·8	873	51·1	425·6
25·0	107·2	30·0	13·77	30·0	26·49	25·8	744·7	54·3	404·6
30·3	95·5	35·6	12·74	39·4	23·33	29·8	662·2	63·1	349·1
35·2	87·3	41·6	11·97	49·3	21·09	30·3	660·0	68·2	327·3
40·0	81·1	46·4	11·53	58·5	19·77	33·2	615·2	72·4	306·9
44·6	75·2	51·0	11·25	65·3	19·05	34·3	606·7	74·7	300·6
49·0	70·5	55·5	11·07	72·5	18·32	34·6	599·8		
54·9	65·5	63·8	10·72	74·9	18·20				
60·2	62·2	72·5	10·54						
65·0	59·2								
72·9	56·1								

In all cases determinations with water as solvent were made at about ten points in the range 12—75°. In the case of salt solutions the aim was to obtain data at temperatures of 12·6°, 30·0°, 49·4°, and 71·7°, corresponding to values of $1/T$ of 0·0035, 0·0033, 0·0031, and 0·0029. In many cases, however, runs at intermediate temperatures confirmed the general tendency of the salting-out results.

The solutions were prepared from "AnalaR" material wherever possible and were

controlled during runs by volumetric methods and density determinations. Small corrections were made in several cases to allow for the fact that the concentrations varied from the desired value of 1 g.-equiv. per 1000 g. of water. In several cases it was shown that the Setschenow equation applied with sufficient accuracy for this correction. In the cases of the multivalent ions Ba^{2+} and La^{3+}, experiments showed that the concentration effect was approximately normal, and that no very different conclusions would be reached by working at unit ionic strength. In the case of hydrogen chloride (with *n*-butane), the concentration effect does not appear to be normal, and further work is proposed on this point. Salting-out values are shown in Table 3.

TABLE 3. *Salting-out constants*, $k = (log\ s_0/s)/c$.

Gas :	*n*-Butane							Propane		
Salt :	NaCl	LiCl	KI	KCl	HCl	½$BaCl_2$	⅓$LaCl_3$	NaCl	LiCl	KI
1/*T*										
0·0035	0·243	0·198	0·109	0·200	0·080	0·250	0·182	0·216	0·175	0·121
0·0033	0·217	0·171	0·098	0·182	0·049	0·210	0·154	0·194	0·152	0·103
0·0031	0·194	0·155	0·080	0·164	0·031	0·180	0·154	0·178	0·138	0·085
0·0029	0·176	0·150	0·059	0·144	0·028	0·165	0·140	0·165	0·138	0·067

Gas :	Ethane			Methane			Hydrogen			
Salt :	NaCl	LiCl	KI	NaCl	LiCl	KI	NaCl	LiCl	KI	⅓$LaCl_3$
1/*T*										
0·0035	0·184	0·155	0·125	0·153	0·130	0·130	0·097	0·064	0·088	0·079
0·0033	0·162	0·124	0·101	0·127	0·097	0·097	0·092	0·065	0·081	0·078
0·0031	0·145	0·110	0·080	0·111	0·082	0·071	0·082	0·061	0·066	0·076
0·0029	0·135	0·107	0·065	0·102	0·077	0·054	0·066	0·054	0·043	0·075

Gas :	Nitrogen			Ethylene			
Salt :	NaCl	LiCl	KI	NaCl	LiCl	KI	⅓$LaCl_3$
1/*T*							
0·0035	0·154	0·125	0·134	0·140	0·104	0·070	0·112
0·0033	0·121	0·095	0·100	0·127	0·089	0·061	0·100
0·0031	0·106	0·084	0·086	0·114	0·082	0·050	0·105
0·0029	0·106	0·092	0·084	0·101	0·083	0·036	0·095

Liquid :	Benzene		Toluene		Ethylbenzene	
	c	*k*	*c*	*k*	*c*	*k*
At 25° in NaCl soln.	0·491	0·195	0·506	0·225	0·508	0·234
	0·755	0·186	0·767	0·213	0·985	0·250
	1·021	0·177	1·002	0·203		
	2·015	0·173	2·022	0·194		

(ii) *Liquid Solubilities.*—The aromatic hydrocarbons were redistilled samples from the purest obtainable material. After an excess of liquid had been shaken with about 1 l. of water at 25°±0·1° for about a week, a known volume of saturated solution was made slightly alkaline, and a stream of pure air passed through to drive off the hydrocarbon. After passage through a silica tube packed with cupric oxide and heated to redness, the water was removed by concentrated sulphuric acid and calcium chloride, and the carbon dioxide absorbed and weighed in soda-asbestos. The precautions usual in organic combustions were taken. The results are the mean of a large number of determinations which varied by about 0·5% for benzene and toluene. Because of the low solubility of ethylbenzene, the error was about 1% in water and about 2% in salt solutions. The solubilities of benzene, toluene, and ethylbenzene were found to be respectively 0·0220, 0·00582, and 0·00155 g.-mol. per 1000 g. of water. Previous measurements (Seidell, "Solubilities of Inorganic and Organic Substances," van Nostrand, N.Y.) give 0·0231 for benzene and 0·00527 for toluene (in the same units). Salting-out was determined over a range of salt concentration (Table 3).

Thanks are offered to the Hallett Trustees for the award of a scholarship to one of us (F. B.).

TECHNICAL COLLEGE, BRIGHTON. [*Received, April 30th*, 1952.]

731. *Triphenylethylenes. Part III.**

By Wadie Tadros and Albert Latif.

A number of triphenylethylene derivatives possessing the dimethylamino-group in the *para*-position of the two phenyl groups on the same ethylenic carbon atom have been synthesised. Two of them showed œstrogenic activity in contrast to the corresponding halogen compounds. Other derivatives also showed œstrogenic activity. Introduction of a halogen atom at the ethylenic linkage did not increase the potency, in contrast to previously tested triphenylethylenes. The quaternary ammonium compounds and stilbenes possessing *p*-dimethylamino-groups were inactive.

In continued study of the effect of substituents on the œstrogenic activity, a number of triphenylethylene derivatives possessing *p*-dimethylamino-groups have been prepared and tested.

1 : 1-Bis-*p*-dimethylaminophenyl-2-phenylethylene was obtained by the dehydration of 1 : 1-bis-*p*-dimethylaminophenyl-2-phenylethanol. The latter was obtained by heating Michler's ketone, toluene, and metallic sodium (Rodd and Linch, *J.*, 1927, 2179), or by addition of Michler's ketone to an ethereal solution of excess of benzylmagnesium chloride (Madelung and Volker, *J. pr. Chem.*, 1927, **115**, 24; Rodd and Linch, *loc. cit.*). The di-*p*-chloro- and di-*p*-bromo-triphenylethylenes were similarly obtained. 4 : 4'-Di-*cyclo*hexyloxy- and 4-dimethylamino-4'-methoxy-benzophenone with benzylmagnesium chloride gave the corresponding alcohols, and the methoxy-compound was dehydrated to the ethylene.

Triphenylbromoethylenes containing dimethylamino-groups were obtained by bromination of the corresponding ethylenes and, in view of the result obtained on testing their œstrogenic activity, their structure was confirmed by ozonolysis.

4-Bromo-4'-dimethylaminostilbene (Haddow, Harris, Kon, and Roe, *Proc. Roy. Soc.*, 1948, *A*, **241**, 147) was prepared by reduction of 4-bromo-4'-nitrostilbene, followed by methylation and decomposition of the quaternary product. Haddow *et al.* (*loc. cit.*) noted that this stilbene could not be obtained by condensation of *p*-bromobenzylmagnesium bromide and *p*-dimethylaminobenzaldehyde. We obtained it by the dehydration of the corresponding alcohol which we prepared in almost quantitative yield by use of an excess of Grignard reagent. The alcohol was dehydrated by phosphoric oxide in hot anhydrous benzene or when heated alone at 155—160°.

The time required for the œstrogenic activity to fall to half was measured as described by Robson (*Quart. J. Exp. Physiol.*, 1938, **28**, 195) with Shorr's method of staining (*Science*, 1940, **91**, 579). The compounds were dissolved in sesame oil and examined by injection subcutaneously into 20—25-g. mice. The œstrogenic table shows that: (*a*) Whereas the stilbenes (8) and (9) have no œstrogenic activity, the triphenylethylenes possessed considerable activity at the same dose (Haddow *et al.*, *loc. cit.*, stated that amino-stilbenes, including compound 8, appeared to have no œstrogenic activity but the dose was not reported; Baker, *J. Amer. Chem. Soc.*, 1943, **65**, 572, reported that the amino-analogue of hexœstrol—3 : 4-bis-*p*-aminophenylhexane—was inactive in both the *meso*- and the racemic form), (*b*) In contrast to the inactivity of triphenylethylenes or their bromo-derivatives containing *p*-halogen atoms in the two phenyl groups on the same ethylenic carbon atom (Schönberg, Robson, Tadros, and Fahim, *J.*, 1940, 1327), the corresponding dimethylamino-compounds are active. (*c*) Whereas the introduction of the halogen atom at the ethylene double bond in many triphenylethylenes was accompanied by considerable increase in œstrogenic activity (see Tadros and Aziz, *J.*, 1951, 2553) the introduction of bromine as in compounds (5—7) did not appreciably increase the potency. (*d*) Comparison of compounds (4) with 1 : 1-di-p-methoxyphenyl-2-phenylethylene (Schönberg *et al.*, *loc. cit.*) showed that the replacement of the methoxy- by the dimethylamino-group decreased the potency.

* Part II, *J.*, 1949, 442.

When injected subcutaneously in solution in saline at the dose of 2 mg., the quaternary ammonium chloride from compound (1) led to death of the mice within 15 minutes. On administration in saline solution at the doses of 5 mg. orally by stomach tube, this salt was

Time required for œstrogenic activity to fall to half.

No.	Compound	Dose (mg.)	Time (days)
1	1 : 1-Bis-*p*-dimethylaminophenyl-2-phenylethylene	5	15
2	2-*p*-Chlorophenyl-1 : 1-bis-*p*-dimethylaminophenylethylene	5	15
3	2-*p*-Bromophenyl-1 : 1-bis-*p*-dimethylaminophenylethylene	5	16
4	2-*p'*-Dimethylaminophenyl-2-*p*-methoxyphenyl-1-phenylethylene	0·2	5
5	2-Bromo-1 : 1-bis-*p*-dimethylaminophenyl-2-phenylethylene	5	19
6	2-Bromo-2-*p*-chlorophenyl-1 : 1-bis-*p*-dimethylaminophenylethylene	5	18
7	2-Bromo-2-*p*-bromophenyl-1 : 1-bis-*p*-dimethylaminophenylethylene	5	17
8	4-Bromo-4'-dimethylaminostilbene	5	Inactive
9	4 : 4'-Bisdimethylaminostilbene *	5	Inactive

* Tadros and Ekladious, unpublished.

inactive. The loss of œstrogenic activity on conversion into the quaternary salt compares with that when aminostilbenes showing growth-inhibitory and carcinogenic properties were converted into their quaternary ammonium salts (Haddow *et al.*, *loc. cit.*).

The triphenylethylene bases are not toxic at doses of 5 mg. and are being tested for chemotherapeutic (*e.g.*, antitubercular) activity in collaboration with Professor S. El Kholy (Ibrahim Pasha University).

Experimental

M. p.s are uncorrected. Microanalysis was carried out by Drs. Weiler and Strauss of Oxford.

1 : 1-*Bis*-p-cyclo*hexyloxyphenyl*-2-*phenylethanol*.—To the Grignard reagent from benzyl chloride (3·8 g.), ether (100 c.c.), and magnesium (0·7 g.), 4 : 4'-di*cyclo*hexyloxybenzophenone (2 g.) (Tadros and Latif, *J.*, 1949, 3337) in benzene (10 c.c.) was added and the mixture was refluxed for 3 hours and then decomposed with aqueous ammonium chloride. Ether extracted the *alcohol* which separated from ethanol in colourless crystals, m. p. 112° (70%) (Found: C, 81·4; H, 8·1. $C_{32}H_{38}O_2$ requires C, 81·7; H, 8·2%).

1-p-*Dimethylaminophenyl*-1-p-*methoxyphenyl*-2-*phenylethanol*, similarly prepared, had m. p. 169° (yield 70%) (Found: C, 79·6; H, 7·6; N, 4·2. $C_{23}H_{25}O_2N$ requires C, 79·5; H, 7·2; N, 4·0%).

1-p-*Dimethylaminophenyl*-1-p-*methoxyphenyl*-2-*phenylethylene*.—The corresponding alcohol was dehydrated by heating it under reflux for 1 hour with 2N-hydrochloric acid. The product was cooled, neutralised with sodium carbonate, and filtered off (almost quantitative yield). The *ethylene* separated from methyl alcohol–acetone in pale yellow crystals, m. p. 162—163° (Found: C, 83·4; H, 7·2; N, 4·6. $C_{23}H_{23}ON$ requires C, 83·8; H, 7·0; N, 4·3%).

The following were isolated in yellowish-green crystals (*ca.* 60%) from benzene–light petroleum (b. p. 40—60°), on attempting the preparation of the corresponding alcohols as above: 2-p-*chlorophenyl*-, m. p. 154° (Found: C, 76·1; H, 6·4; N, 7·7; Cl, 9·9. $C_{24}H_{25}N_2Cl$ requires C, 76·5; H, 6·6; N, 7·4; Cl, 9·5%), and 2-p-*bromophenyl*-1 : 1-*bis*-p-*dimethylaminophenylethylene*, m. p. 159° (Found: C, 68·4; H, 5·8; N, 6·2; Br, 17·9. $C_{24}H_{25}N_2Br$ requires C, 68·4; H, 5·9; N, 6·6; Br, 18·3%).

Triphenylbromoethylenes.—An ice-cold solution of bromine (1 mol.) in the minimum amount of benzene was added all at once to a cooled benzene solution of the ethylene (1 mol.). A dark brown material separated immediately. The reaction mixture was shaken with 10% sodium hydroxide solution and extracted with more benzene (yield almost theoretical). Thus were obtained 1-*bromo*-2 : 2-*bis*-p-*dimethylaminophenyl*-1-*phenylethylene*, yellow, m. p. 185—186° (from benzene–alcohol) (Found: Br, 18·9. $C_{24}H_{25}N_2Br$ requires Br, 19·0%), 1-*bromo*-1-p-*chlorophenyl*-, yellow, m. p. 158—160° (from benzene–methyl alcohol) (Found: Hal, 24·8. $C_{24}H_{24}N_2BrCl$ requires Hal, 25·4%), and 1-*bromo*-1-p-*bromophenyl*-2 : 2-*bis*-p-*dimethylaminophenylethylene*, greenish-yellow, sinters at 170°, m. p. 177° (from acetone–methyl alcohol) (Found: Br, 31·8. $C_{24}H_{24}N_2Br_2$ requires Br, 32·0%).

Ozonolysis. A stream of dry ozonised oxygen (3%) was passed through a cold solution of the bromoethylene in carbon tetrachloride until the reaction was almost complete. The solution was shaken with water (removed hydrogen bromide) and evaporated and the residue was treated with 10% sodium hydroxide solution and filtered. The filtrate was acidified and the precipitated acid crystallised from alcohol. The alkali-insoluble material crystallised from

dilute alcohol. 1-Bromo-2 : 2-bis-*p*-dimethylaminophenyl-1-phenylethylene gave benzoic acid, m. p. and mixed m. p. 120°, and Michler's ketone, m. p. and mixed m. p. 173°. 1-Bromo-1-*p*-bromophenyl-2 : 2-bis-*p*-dimethylaminophenylethylene gave *p*-bromobenzoic acid, m. p. and mixed m. p. 249—250°, and Michler's ketone. 1-Bromo-1-*p*-chlorophenyl-2 : 2-bis-*p*-dimethylaminophenylethylene gave *p*-chlorobenzoic acid, m. p. and mixed m. p. 234—235°, and Michler's ketone.

Quaternary Ammonium Salts.—The *salts* listed in the Table were prepared in the usual way. All are soluble in water and alcohol, but completely insoluble in ether, benzene, or acetone. The chlorides, bromides, and iodides are hygroscopic and retain solvent of crystallisation (particularly alcohol) which can only be removed by heating at 100°/vac. for a considerable time over phosphoric oxide or calcium chloride. They were generally crystallised from ethanol or methanol, with or without acetone or ether.

		Found, %					Required, %			
Salt [a]	M. p.[b]	C	H	N	Hal.		C	H	N	Hal.
1 : 1-*Bis*-p-*dimethylaminophenyl*-2-*phenylethylene salts.*										
A	220°	55·0	4·3	13·3	—	$C_{38}H_{36}O_{14}N_8$	55·1	4·3	13·5	—
B	204—205	69·9	6·9	6·9	15·6	$C_{26}H_{32}N_2Cl_2$	70·4	7·2	6·3	16·0
C	176—177	58·4	6·0	4·7	31·0	$C_{26}H_{32}N_2Br_2$	58·6	6·0	5·3	30·1
D [c]	198—200	50·1	5·5	4·5	40·5	$C_{26}H_{32}N_2I_2$	49·8	5·1	4·5	40·6
E	266	54·6	5·8	5·1	12·3	$C_{26}H_{32}O_6N_2Cl_2$	54·6	5·6	4·9	12·4
2-p-*Chlorophenyl*-1 : 1-*bis*-p-*dimethylaminophenylethylene salts.*										
A	187	52·6	4·0	13·1	4·0	$C_{38}H_{35}O_{14}N_8Cl$	52·9	4·1	13·0	4·1
B	163—164	65·1	6·5	5·8	22·1	$C_{26}H_{31}N_2Cl_3$	65·3	6·5	5·9	22·3
C	174—176	54·9	5·3	4·9	34·2	$C_{26}H_{31}N_2Br_2Cl$	55·1	5·5	4·9	34·5
D	220	47·0	4·5	4·1	43·5	$C_{26}H_{31}N_2ClI_2$	47·2	4·7	4·2	43·9
E	268	51·4	5·2	4·7	17·6	$C_{26}H_{31}O_6N_2Cl_3$	51·5	5·1	4·6	17·5
2-p-*Bromophenyl*-1 : 1-*bis*-p-*dimethylaminophenylethylene salts.*										
A	189—190	50·6	4·0	12·5	8·5	$C_{38}H_{35}O_{14}N_8Br$	50·3	3·9	12·3	8·8
B	180—182	59·5	5·8	5·4	28·5	$C_{26}H_{31}N_2Cl_2Br$	59·7	5·9	5·4	28·8
C	193	51·0	4·8	4·8	38·9	$C_{26}H_{31}N_2Br_3$	51·1	5·1	4·6	39·5
D	224	44·5	4·5	3·8	47·6	$C_{26}H_{31}N_2BrI_2$	44·2	4·4	4·0	47·4
E	286	48·4	4·6	4·2	22·9	$C_{26}H_{31}O_6N_2Cl_2Br$	48·0	4·8	4·3	23·2

[a] A, Picrate; B, chloride; C, bromide; D, iodide; E, perchlorate. [b] With decomp. (except for picrates). [c] Kehlstadt (*Helv. Chim. Acta*, 1944, **27**, 683) gave m. p. 195°.

Decomposition of Quaternary Salts.—The salt (5 g.) and methanolic sodium methoxide (2·5 atomic equivs. of sodium in 20 c.c. of methanol) was heated for 4 hours on the water-bath. Methyl alcohol was distilled off and the residue treated with concentrated hydrochloric acid (1 : 1), whereby a clear solution was obtained. The bases, precipitated by sodium hydroxide, crystallised from alcohol and were proved by their m. p.s and mixed m. p.s to be the tertiary bases.

2-p-*Bromophenyl*-1-p-*dimethylaminophenylethanol.*—To a Grignard reagent, prepared from *p*-bromobenzyl bromide (40 g.), magnesium (4·8 g.), and dry ether (350 c.c.), *p*-dimethylaminobenzaldehyde (6 g.) was added and the solution stirred for 2 hours, left overnight, and then decomposed with aqueous ammonium chloride. Ether extracted the alcohol and the ethereal solution was washed with 18% hydrochloric acid. The acid solution was diluted, filtered, and made alkaline with aqueous ammonia. The *alcohol* separated from ethanol in pale yellow crystals which sintered at 114° and melted at 117° (yield, almost 100%) (Found : C, 60·8; H, 5·6; N, 4·2; Br, 25·1. $C_{16}H_{18}ONBr$ requires C, 60·0; H, 5·6; N, 4·4; Br, 25·0%).

4-*Bromo*-4'-*dimethylaminostilbene.*—(*a*) A mixture of the foregoing alcohol (2 g.), phosphoric oxide (2 g.), and benzene (50 c.c.) was refluxed for 2 hours. After cooling, the solution was filtered. The residue was decomposed with water and the stilbene was filtered off. It separated from benzene and had m. p. 231—232° (yield, almost 100%) (Found : C, 63·5; H, 5·0; N, 4·4; Br, 26·2. Calc. for $C_{16}H_{16}NBr$: C, 63·5; H, 5·3; N, 4·6; Br, 26·5%).

(*b*) When the alcohol (2 g.) was heated, water was evolved at 155° and the material solidified within 1 minute at 155—160°, to give the stilbene.

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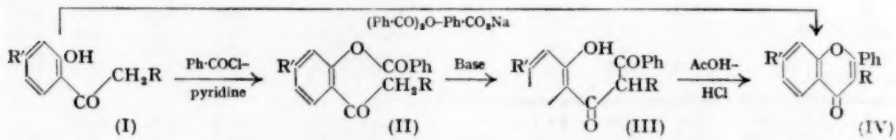
732. *The Synthesis of* 3-*Substituted Chromones by Rearrangement of* o-*Acyloxyacetophenones.*

By W. D. Ollis and D. Weight.

The base-catalysed rearrangement of *o*-acyloxyacetophenones (II) (the Baker–Venkataraman transformation) has been extended to ω-methyl, ω-methoxy, and ω-phenyl derivatives. The resulting 1 : 3-diketones (III) gave 3-substituted chromones (IV) with hydrochloric acid in acetic acid. Similar rearrangement and cyclisation of *o*-furoyloxy- or *o*-acetoxy-acetophenone (*e.g.*, VI) gave 2-substituted chromones (VIII).

The base-catalysed rearrangement of *o*-acyloxyacetophenones (*e.g.*, II; R = H) to *o*-hydroxydibenzoylmethanes (*e.g.*, III; R = H) (the Baker–Venkataraman transformation) (Baker, *J.*, 1933, 1381; 1934, 1953; Venkataraman *et al.*, *J.*, 1934, 1767; 1935, 868; Wheeler *et al.*, *Proc. Roy. Irish Acad.*, 1948, **24**, 291, where references to previous work are given) has been extended to ω-substituted acetophenones (*e.g.*, II; R = Me, OMe, or Ph). 3-Methoxyflavones (and thence flavonols) and *iso*flavones may thus be prepared.* These substances have usually been prepared by the Allan–Robinson synthesis (*e.g.*, I ⟶ IV), and the present work confirmed the view that the Baker–Venkataraman rearrangement is probably involved in this method.



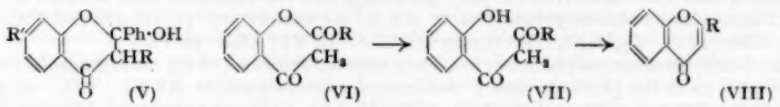
The *O*-benzoate (II; R = Me, R′ = OMe) of 2-hydroxy-4-methoxypropiophenone (I; R = Me, R′ = OMe) was smoothly rearranged by potassium hydroxide in pyridine to the 1 : 3-diketone (III; R = Me, R′ = OMe), which cyclised to 7-methoxy-3-methylflavone (IV; R = Me; R′ = OMe) when warmed with acetic–hydrochloric acids. Similarly, 2 : 4-dibenzoyloxypropiophenone (II; R = Me, R′ = Ph·CO·O) gave the diketone (III; R = Me; R′ = Ph·CO·O), and thence 7-benzoyloxy-3-methylflavone (IV; R = Me; R′ = Ph·CO·O). Demethylation of 7-methoxy-3-methylflavone, or hydrolysis of 7-benzoyloxy-3-methylflavone, gave 7-hydroxy-3-methylflavone (IV; R = Me; R′ = OH) (Canter, Curd, and Robertson, *J.*, 1931, 1264).

Rearrangement of 2-benzoyloxy-4 : ω-dimethoxyacetophenone (II; R = R′ = OMe) was not satisfactorily achieved although a variety of basic agents was used. The attempted isomerisation of 2 : 4-dibenzoyloxy-ω-methoxyacetophenone (II; R = OMe; R′ = Ph·CO·O) with potassium hydroxide in pyridine resulted in hydrolysis of the 1 : 3-diketone, but with potassium ethoxide in pyridine gave 4-benzoyloxy-2-hydroxy-ω-methoxyacetophenone (I; R = OMe, R′ = Ph·CO·O) formed by simple hydrolysis and the expected dibenzoylmethane derivative (III; R = OMe, R′ = Ph·CO·O). This 1 : 3-diketone could not be crystallised, but was readily cyclised with acetic–hydrochloric acids to 7-benzoyloxy-3-methoxyflavone (IV; R = OMe, R′ = Ph·CO·O), which on hydrolysis gave 7-hydroxy-3-methoxyflavone identical with that prepared by Allan and Robinson (*J.*, 1924, **125**, 2194). Wheeler *et al.* (*J.*, 1950, 1258) have similarly prepared 7-benzoyloxy-3-methoxyflavone by heating 2 : 4-dibenzoyloxy-ω-methoxyacetophenone in pyridine with potassium carbonate.

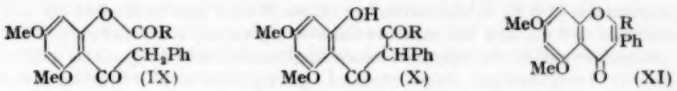
Wheeler *et al.* (*J.*, 1950, 1254) reported that *o*-acetoxyacetophenone (VI; R = Me) could not be isomerised to 2-acetoacetylphenol (VII; R = Me) by the bases usually employed, *e.g.* potassium hydroxide in pyridine or metallic sodium in toluene, but that triphenylmethylsodium was effective. We, however, found use of potassium hydroxide in

* Since this paper was submitted for publication, Lynch, O'Toole, and Wheeler (*J.*, 1952, 2063) have described the preparation of flavanol 3-methyl ethers by thermal cyclisation (involving Baker–Venkataraman transformations) of aroyl esters of ω-methoxyphloracetophenones.

pyridine as successful as that of triphenylmethylsodium. This transformation also occurs when sodium in benzene is used (Virkar and Shah, *Proc. Indian Acad. Sci.*, **1949**, **30**, 58). Also *o*-2′-furoyloxyacetophenone (VI; R = 2-furyl) with potassium hydroxide in pyridine gives 2′-furoyl-*o*-hydroxybenzoylmethane (VII; R = 2-furyl), and thence 2-2′-furylchromone (VIII; R = 2-furyl), which is unaffected by boiling hydrobromic–acetic acid.



Rearrangement of 2-acyloxydeoxybenzoins has not been studied previously and is of interest in connection with the synthesis of *iso*flavones. 2-Benzoyloxy-4 : 6-dimethoxydeoxybenzoin (IX; R = Ph) was readily converted by potassium hydroxide in pyridine into the 1 : 3-diketone (X; R = Ph), which was cyclised in the usual way to 5 : 7-dimethoxy-2 : 3-diphenylchromone (XI; R = Ph). This chromone when demethylated gave 5 : 7-dihydroxy-2 : 3-diphenylchromone, identical with the compound prepared previously (Baker and Eastwood, *J.*, 1929, 2901) by fusion of 2 : 4 : 6-trihydroxydeoxybenzoin with benzoic anhydride and sodium benzoate, and subsequent hydrolysis. Baker (*J.*, 1933, 1388) described the formation of 7-hydroxy-2 : 3-diphenylchromone when 2 : 4-dihydroxydeoxybenzoin is heated with benzoyl chloride and potassium carbonate in toluene. A rearrangement is probably involved in this and the preceding experiment.



Similarly, 2-2′-furoyloxy-4 : 6-dimethoxydeoxybenzoin (IX; R = 2-furyl) gave the diketone (X; R = 2-furyl) and thence 2-2′-furyl-4 : 6-dimethoxy*iso*flavone (XI; R = 2-furyl). We failed to oxidise this to 4 : 6-dimethoxy*iso*flavone-2-carboxylic acid (X; R = CO_2H).

It is of interest that all the diketones of the type (III) where R = Me, OMe, or Ph are colourless, whereas those in which R = H are bright yellow. This difference may be due either to alteration in the degree of enolisation or to disturbance of the (probable) equilibrium between (III) and its hemi-acetal (V). That (V) as well as (III) is probably concerned in the actual equilibrium structure of these diketones is indicated by their relatively weak ferric chloride reactions and their slow rate of solution in alkali in some cases. In this connection, it is perhaps significant that, when first prepared, (III; R = Me; R′ = OMe) had m. p. 166°, but, on keeping or recrystallisation, the m. p. fell to 134°; similar examples are given by Baker, Ollis, and Poole (*J.*, 1952, 1505).

Experimental

M.p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford, and Mr. W. M. Eno, Bristol.

2-Hydroxy-4-methoxypropiophenone (I; R = Me; R′ = OMe).—2 : 4-Dihydroxypropiophenone (50 g.), anhydrous benzene (500 c.c.), freshly roasted potassium carbonate (50 g.), and methyl sulphate (38 g.) were boiled for 10 hours, cooled, and filtered, and the solid was washed with hot benzene. Removal of the benzene left a residue which, crystallised from ethanol (30 c.c.), gave 2-hydroxy-4-methoxypropiophenone (39 g., 72%), m. p. 56° (Tahara, *Ber.*, **1892**, **25**, 1298, records m. p. 58°). Methylation by Adams's procedure for the preparation of 2-hydroxy-4-methoxyacetophenone (*J. Amer. Chem. Soc.*, **1919**, **41**, 260) gave a 50—55% yield, but distillation (b. p. 118—124°/0·3 mm.) was necessary to obtain a satisfactory product.

2-Hydroxy-4 : ω-dimethoxyacetophenone (I; R = R′ = OMe).—Monomethylation of 2 : 4-dihydroxy-ω-methoxyacetophenone according to Slater and Stephen (*J.*, 1920, 313) gave only a 20% yield in our hands. The following method gave a 78% yield.

2 : 4-Dihydroxy-ω-methoxyacetophenone (11·1 g.; Slater and Stephen, *loc. cit.*), anhydrous benzene (300 c.c.), freshly roasted potassium carbonate, and methyl sulphate (7·7 g.) were boiled for 10 hours, filtered, and the solid washed with hot benzene. The filtrate and washings after

concentration yielded 2-hydroxy-4 : ω-dimethoxyacetophenone (9·4 g.), m. p. 66° (Slater and Stephen gave m. p. 66°).

Preparation of ω-Substituted o-Benzoyloxyacetophenones (II).—(*a*) 2-Hydroxy-4-methoxypropiophenone (20 g.), dry pyridine (30 c.c.), and benzoyl chloride (15·6 g.) were heated on a steam-bath for 15 minutes, cooled, and poured into dilute hydrochloric acid. The precipitated oil solidified and was washed, dried (28·5 g., 90%), and recrystallised from ethanol (50 c.c.), giving *2-benzoyloxy-4-methoxypropiophenone* (18 g.) as needles, m. p. 48° (Found: C, 71·6; H, 5·5; OMe, 10·9. $C_{16}H_{13}O_3$·OMe requires C, 71·8; H, 5·6; OMe, 10·9%).

(*b*) 2 : 4-Dihydroxypropiophenone (10 g.) and benzoyl chloride (16·9 g.) in anhydrous pyridine (25 c.c.) gave as in the previous case 2 : 4-*dibenzoyloxypropiophenone* (18·2 g., 86%), m. p. 92°, needles from methanol (50 c.c.) (Found: C, 73·5; H, 4·8. $C_{23}H_{18}O_5$ requires C, 73·8; H, 4·8%).

(*c*) 2-Hydroxy-4 : ω-dimethoxyacetophenone (3 g.) and benzoyl chloride (2·15 g.) in anhydrous pyridine (5 c.c.) were kept at room temperature for 2 hours and poured into dilute hydrochloric acid. The oil which solidified was collected (2·3 g., 50%) and crystallised from ethanol (10 c.c.), giving *2-benzoyloxy-4 : ω-dimethoxyacetophenone* (1·8 g.) as needles, m. p. 43° (Found: C, 67·8; H, 5·2. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%). This compound could not be satisfactorily rearranged to give the corresponding diketone (see below).

2-Benzoyloxy-4 : 6-dimethoxydeoxybenzoin (IX; R = Ph).—2-Hydroxy-4 : 6-dimethoxydeoxybenzoin (7 g.; Badcock, Cavill, Robertson, and Whalley, *J.*, 1950, 2964) and benzoyl chloride (3·7 g.) in pyridine (12 c.c.) gave, as in the preceding cases, after 15 minutes' heating, *2-benzoyloxy-4 : 6-dimethoxydeoxybenzoin* (8·45 g.; 87%) as needles, m. p. 94°, from chloroform or ethyl acetate (30 c.c.) (Found: C, 73·4; H, 5·1. $C_{23}H_{20}O_5$ requires C, 73·4; H, 5·3%).

α-Benzoyl-2-hydroxy-4-methoxypropiophenone (III; R = Me, R′ = OMe).—2-Benzoyloxy-4-methoxypropiophenone (2·0 g.) in anhydrous pyridine (6 c.c.) was treated at 50° with powdered potassium hydroxide (0·5 g.), and the mixture shaken vigorously for 5 minutes. The suspension of the yellow potassium salt of the diketone was added to excess of 20% acetic acid, and the solid (1·4 g., 70%) was recrystallised from ethanol, giving *α-benzoyl-2-hydroxy-4-methoxypropiophenone* (1·2 g.) as colourless cubes, m. p. 134° (Found: C, 71·7; H, 5·8; OMe, 11·1. $C_{16}H_{13}O_3$·OMe requires C, 71·8; H, 5·7; OMe, 10·9%). This compound when first prepared had m. p. 166° (cf. p. 3827); the m. p. 144° recorded for this compound by Baker, Ollis, and Poole (*loc. cit.*) was given in error for 134°. The diketone slowly dissolved in 2N-sodium hydroxide and gave a fairly weak reddish-brown colour with aqueous-alcoholic ferric chloride.

α-Benzoyl-4-benzoyloxy-2-hydroxypropiophenone (III; R = Me, R′ = Ph·CO·O) and *4-Benzoyloxy-2-hydroxypropiophenone* (I; R = Me, R′ = Ph·CO·O).—As in the preceding experiment, 2 : 4-dibenzoyloxypropiophenone (10 g.) in pyridine (25 c.c.) with potassium hydroxide (1·6 g.) gave an oil (7·1 g.) on being poured into excess of dilute acetic acid. It could not be crystallised, but its constitution as α-benzoyl-4-benzoyloxy-2-hydroxypropiophenone follows from its ready conversion into 7-benzoyloxy-3-methylflavone by hydrochloric acid in glacial acetic acid (see below).

In an attempt to purify this diketone, a portion was distilled (b. p. 210—220°/0·4 mm.), and the product was identified as *4-benzoyloxy-2-hydroxypropiophenone* (I; R = Me, R′ = Ph·CO·O), colourless needles, m. p. 80° (Found: C, 71·0; H, 5·3. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%). It gave a strong purple ferric chloride reaction. The distillation residue crystallised from methanol, giving 7-benzoyloxy-3-methylflavone, m. p. and mixed m. p. 127° (see below).

α-Benzoyl-4-benzoyloxy-2-hydroxy-α-methoxyacetophenone (III; R = OMe, R′ = Ph·CO·O) *and 4-Benzoyloxy-2-hydroxy-ω-methoxyacetophenone* (I; R = OMe, R′ = Ph·CO·O).—The rearrangement was attempted with potassium hydroxide but extensive hydrolysis occurred; use of potassium ethoxide was more successful. Potassium ethoxide (1·2 g.) was added at room temperature to a solution of 2 : 4-dibenzoyloxy-ω-methoxyacetophenone (5 g.; Fonseka, *J.*, 1947, 1683) in anhydrous pyridine (20 c.c.). A bright yellow precipitate separated and after 1 minute excess of dilute acetic acid was added. The oil was extracted with chloroform and dried ($MgSO_4$), and the solvent removed, leaving a residue (3·9 g.) which was not obtained completely crystalline. In an attempted purification it was dissolved in hot ethanol, and on cooling *4-benzoyloxy-2-hydroxy-ω-methoxyacetophenone* (0·4 g.) separated as colourless prisms, m. p. 122° (Found: C, 67·1; H, 4·9. $C_{16}H_{14}O_5$ requires C, 67·1; H, 5·2%). It gave a strong purple ferric chloride reaction. Removal of the ethanol from the mother-liquors gave a sticky residue which was at least mainly α-benzoyl-4-benzoyloxy-2-hydroxy-α-methoxyacetophenone as it was readily cyclised to give the corresponding flavone (see below).

α-Benzoyl-2-hydroxy-4 : 6-dimethoxydeoxybenzoin (X; R = Ph).—Powdered potassium hydroxide (0·56 g.) was added to a solution of 2-benzoyloxy-4 : 6-dimethoxydeoxybenzoin (3·7 g.) in anhydrous pyridine (10 c.c.). The required potassium salt separated immediately. The oil

obtained by pouring the mixture into dilute hydrochloric acid solidified (3·6 g., 97%). Crystallisation from ethanol (50 c.c.) gave α-*benzoyl*-2-*hydroxy*-4 : 6-*dimethoxydeoxybenzoin* as colourless prisms, m. p. 180° [Found : C, 73·5; H, 5·5; OMe, 16·6. $C_{21}H_{14}O_3(OMe)_2$ requires C, 73·4; H, 5·3; OMe, 16·5%]. It gave a reddish-brown ferric chloride reaction, but was not soluble in 2N-sodium hydroxide.

7-*Methoxy*-3-*methylflavone* (IV; R = Me, R′ = OMe).—α-Benzoyl-2-hydroxy-4-methoxypropiophenone (6 g.), glacial acetic acid (40 c.c.), and concentrated hydrochloric acid (2 c.c.) were warmed on a steam-bath for 5 minutes, cooled, and diluted with water. The solid (5·1 g., 85%) crystallised from ethanol (25 c.c.), giving 7-*methoxy*-3-*methylflavone* as needles, m. p. 116° (Found : C, 76·7; H, 5·4; OMe, 11·4. $C_{16}H_{11}O_2$·OMe requires C, 76·7; H, 5·3; OMe, 11·6%).

7-*Benzoyloxy*-3-*methylflavone* (IV; R = Me, R′ = Ph·CO·O).—As in the preceding experiment, crude α-benzoyl-4-benzoyloxy-2-hydroxypropiophenone (7·1 g.), acetic acid (20 c.c.), and concentrated hydrochloric acid (1 c.c.) gave 7-benzoyloxy-3-methylflavone (6·3 g., 93%), colourless needles, m. p. 127°, from methanol (150 c.c.) (Found : C, 77·4; H, 4·6. $C_{23}H_{16}O_4$ requires C, 77·5; H, 4·5%).

This and the preceding flavone were each converted into 7-hydroxy-3-methylflavone (IV; R = Me; R′ = OH) as follows. (*a*) 7-Methoxy-3-methylflavone (1 g.), glacial acetic acid (20 c.c.), and hydrobromic acid (20 c.c.; *d* 1·49) were boiled for 8 hours, then diluted with water, and the solid (0·9 g., 95%) was collected. Crystallisation from ethanol (4 c.c.) gave 7-hydroxy-3-methyl flavone as fine needles, m. p. 278°.

(*b*) 7-Benzoyloxy-3-methylflavone (1 g.) and potassium hydroxide (0·28 g.) were dissolved in ethanol (15 c.c.) and water (15 c.c.), boiled for ½ hour, the mixture was diluted with water and saturated with carbon dioxide, and the solid (0·59 g., 84%) collected. Crystallisation from ethanol gave 7-hydroxy-3-methylflavone, m. p. and mixed m. p. 278°. The acetyl derivative, prepared by use of acetic anhydride and pyridine, had m. p. 132° after several crystallisations from ethanol. Canter, Curd, and Robertson (*J.*, 1931, 1264) give m. p. 278° for 7-hydroxy-3-methylflavone, and m. p. 137° for its acetate.

7-*Benzoyloxy*-3-*methoxyflavone* (IV; R = OMe, R′ = Ph·CO·O).—Crude α-benzoyl-4-benzoyloxy-2-hydroxy-α-methoxypropiophenone (2·9 g.), acetic acid (10 c.c.), and concentrated hydrochloric acid (0·5 c.c.) were warmed on a steam-bath for 5 minutes. Addition of water gave an oil, and chloroform-extraction yielded a residue which, after crystallisation from ethanol, gave 7-*benzoyloxy*-3-*methoxyflavone* as colourless needles, m. p. 131° (Found : C, 73·5; H, 4·1. $C_{23}H_{16}O_5$ requires C, 73·4; H, 4·3%).

Alkaline hydrolysis of this flavone (1 g.) as in the case of 7-benzoyloxy-3-methylflavone gave 7-hydroxy-3-methoxyflavone (0·7 g.), colourless needles, m. p. 233°, from ethanol (Allan and Robinson, *J.*, 1924, 2194, give m. p. 227°; Wheeler *et al.*, *J.*, 1950, 1258, give m. p. 233°).

5 : 7-*Dimethoxy*-2 : 3-*diphenylchromone* (XI; R = Ph).—α-Benzoyl-2-hydroxy-4 : 6-dimethoxydeoxybenzoin (0·75 g.), acetic acid (5 c.c.), and concentrated hydrochloric acid (0·3 c.c.), when heated on a steam-bath for 5 minutes, gave 5 : 7-*dimethoxy*-2 : 3-*diphenylchromone* (0·7 g.), colourless rhombs, m. p. 195°, from ethyl acetate (3 c.c.) [Found : C, 77·1; H, 5·2; OMe, 17·5. $C_{21}H_{12}(OMe)_2$ requires C, 77·1; H, 5·1; OMe, 17·3%].

This chromone (0·3 g.), acetic acid (6 c.c.), and hydrobromic acid (6 c.c.; *d* 1·49) were boiled for 8 hours. Addition of water gave a solid (0·2 g.) which, after crystallisation from ethanol, gave 5 : 7-dihydroxy-2 : 3-diphenylchromone, m. p. 250°. It showed no depression of m. p. when mixed with a specimen prepared by the method of Baker and Eastwood (*J.*, 1929, 2901) and gave a gel with 1% aqueous sodium hydroxide (cf. Baker and Eastwood).

o-*Acetoacetylphenol* (VII; R = Me).—To *o*-acetoxyacetophenone (VI; R = Me) (4·2 g.; Friedländer and Neudörfer, *Ber.*, 1897, **30**, 1080) in anhydrous pyridine (10 c.c.) powdered potassium hydroxide (1 g.) was added with stirring at room temperature. After 15 minutes, dilute hydrochloric acid was added and the solution set aside in the refrigerator; the crystalline precipitate which separated was recrystallised from benzene–light petroleum (b. p. 60—80°), giving *o*-acetoacetylphenol (0·3 g., 7%) as needles, m. p. and mixed m. p. with an authentic specimen, 92° (Wittig, *Annalen*, 1926, **446**, 169, gives m. p. 90·5—91·5°). The yield is slightly higher than that obtained by Wheeler *et al.* (*J.*, 1950, 1255) who used triphenylmethylsodium. Virkar and Shah (*Proc. Indian Acad. Sci.*, 1949, **30**, 58) reported that this rearrangement may also be effected with sodium in benzene, but the yield was poor and isolation of the product *via* its copper derivative was necessary.

o-2′-*Furoyloxyacetophenone* (VI; R = 2-furyl).—2-Furoyl chloride (5·5 g.) was added to *o*-hydroxyacetophenone (5·6 g.) in dry pyridine (10 c.c.), and after 1 hour the whole was poured into dilute hydrochloric acid. The solid (9·4 g., 99%) crystallised from ethanol, giving *o*-2′-

furoyloxyacetophenone as colourless plates, m. p. 92° (Found : 67·8; H, 4·2. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·3%).

2-2′-*Furoyloxy*-4 : 6-*dimethoxydeoxybenzoin* (IX; R = 2-furyl).—Similarly, 2-furoyl chloride (2·5 g.) and 2-hydroxy-4 : 6-dimethoxydeoxybenzoin (5 g.) in pyridine (20 c.c.) gave the **2-2′-*furoyloxy*-4 : 6-*dimethoxydeoxybenzoin*** (6·1 g., 91%), as colourless platelets, m. p. 116°, from ethanol (Found : C, 68·9; H, 4·8. $C_{21}H_{18}O_6$ requires C, 68·8; H, 4·9%).

2-*Furoyl*-o-*hydroxybenzoylmethane* (VII; R = 2-furyl).—Powdered potassium hydroxide (4·4 g.) was slowly added to ***o*-2′-**furoyloxyacetophenone (15·2 g.) in dry pyridine (40 c.c.). After 5 minutes, excess of dilute acetic acid was added, and the oil which solidified was collected (9·9 g., 65%) and crystallised from ethanol, giving **2-*furoyl*-o-*hydroxybenzoylmethane*** (8·8 g.) as yellow needles, m. p. 76° (Found : C, 67·8; H, 4·2. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·3%). It gave a yellow solution in aqueous sodium hydroxide and an intense reddish-brown colour with aqueous-alcoholic ferric chloride.

α-2″-*Furoyl*-2-*hydroxy*-4 : 6-*dimethoxydeoxybenzoin* (X; R = 2-furyl).—Similarly, powdered potassium hydroxide (0·7 g.) and 2-2″-furoyloxy-4 : 6-dimethoxydeoxybenzoin (4·4 g.) in pyridine (20 c.c.) after 5 minutes at 50° gave **α-2″-*furoyl*-2-*hydroxy*-4 : 6-*dimethoxydeoxybenzoin*** (4·1 g., 93%) as colourless prisms, m. p. 139°, from ethanol (15 c.c.) (Found : C, 68·5; H, 5·2. $C_{21}H_{18}O_6$ requires C, 68·8; H, 4·9%). It gave a deep-red ferric chloride reaction and gave a yellow solution in 2N-sodium hydroxide.

2-2′-*Furylchromone* (VIII; R = 2-furyl).—α-2′-Furoyl-*o*-hydroxybenzoylmethane (2·5 g.), acetic acid (10 c.c.), and concentrated hydrochloric acid (0·5 c.c.) gave, after 5 minutes at 100°, **2-2′-*furylchromone*** (2·1 g., 91%). This forms colourless needles, m. p. 135°, from ethanol (10 c.c.) (Found : C, 73·3; H, 3·7. $C_{13}H_8O_3$ requires C, 73·6; H, 3·8%).

2-2′-*Furyl*-5 : 7-*dimethoxy*isoflavone (XI; R = 2-furyl).—Similarly α-2″-furoyl-2-hydroxy-4 : 6-dimethoxydeoxybenzoin (2 g.) gave **2-2′-*furyl*-5 : 7-*dimethoxy*isoflavone** (1·9 g.), fine, colourless needles, m. p. 195°, from ethanol (10 c.c.) (Found : C, 72·4; H, 4·5. $C_{21}H_{16}O_5$ requires C, 72·4; H, 4·6%).

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733. *Organic Fluorides. Part XIII.* The High-temperature Dimerisation of Chlorotrifluoroethylene.*

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Chlorotrifluoroethylene, when passed through a tube packed with Pyrex glass chips at about 700°, is converted into a complex mixture of products, the chief of which is 1 : 2-dichlorohexafluoro*cyclo*butane. This product is formed also when the olefin is heated at 200° under high pressures. By dechlorination, the cyclic dimer is converted into perfluoro*cyclo*butene; this gives the corresponding 1 : 2-dibromo-compound with bromine, and, by oxidation with aqueous permanganate, tetrafluorosuccinic acid.

PART of the programme of work on organic fluoro-compounds in progress in this department a few years ago was a study of fluorinated olefins and the derived polymers. At that time one of the few readily available aliphatic fluoro-derivatives was 1 : 1 : 2-trichloro-1 : 2 : 2-trifluoroethane, which may be prepared by treatment of hexachloroethane with antimony trifluoride (Booth, Mong, and Burchfield, *Ind. Eng. Chem.*, 1932, **24**, 328; Locke, Brode, and Henne, *J. Amer. Chem. Soc.*, 1934, **56**, 1726). It is dechlorinated by zinc dust in boiling ethyl alcohol to give chlorotrifluoroethylene (Booth, Burchfield, Bixby, and McKelvey, *ibid.*, 1933, **55**, 2231; Locke, Brode, and Henne, *loc. cit.*). This olefin may be polymerised to give medium- and long-chain products, as was first reported in patents issued to I. G. Farben. A.-G. (Fr. P. 796,026, B.P. 465,520, G.P. 677,071). The polymers have been studied extensively in the U.S.A. [Miller, Dittman, Ehrenfeld, and Prober, *Ind. Eng. Chem.*, 1947, **39**, 333; Belmore, Ewalt, and Wojcik, *ibid.*, p. 338; for a full report

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of the work by Miller and his many co-workers see the chapter by Miller in " Preparation, Properties, and Technology of Fluorine and Organic Fluoro-compounds " (Editors, Slesser and Schram), McGraw-Hill, New York, 1951, p. 567], and we have carried out similar (unpublished) investigations in collaboration with workers of Imperial Chemical Industries Limited, Dyestuffs Division, Blackley.

In addition to this type of reaction we investigated the possibility of using chlorotrifluoroethylene and trichlorotrifluoroethane for the synthesis of other fluoro-compounds and, since attempts at Wurtz-type reactions were unsuccessful, attention was turned to possible short-chain polymerisations of chlorotrifluoroethylene. It was found that the olefin could be dimerised by heat, a *cyclo*butane derivative being the principal product; this paper describes these investigations.

The first experiments on the thermal dimerisation of chlorotrifluoroethylene were carried out by passing the olefin through an iron tube packed with copper turnings and heated to various temperatures. Variations tried were the use of gold-plated copper turnings, Pyrex glass chips, and nickel chips as packings in Pyrex glass tubes which, though some softening and deformation occurred, could be used with care at about 700°. These early experiments showed that at temperatures below 620° most of the chlorotrifluoroethylene could be recovered unchanged, whereas, at 800° or above, complete decomposition occurred; but between 680° and 730° a mixture of products was formed, most of which had boiling points between 18° and 100°. Of the materials tested, the best packing for the tube appeared to be Pyrex glass chips. Further, it was noticed that during several successive runs through a tube, the surface of the glass packing gradually became etched and that this coincided with a steady increase in the yield of products boiling higher than the starting material. Accordingly, some glass packing was etched by treatment with potassium fluoride and sulphuric acid before use, and, compared with ordinary unetched Pyrex chips, the yield of high-boiling product was considerably increased.

Treatment of the fractions of the pyrolysis product having b. p. 50—100° with zinc dust and ethyl alcohol gave a product, b. p. 0—10°, which could not be purified, but which appeared to be an impure fluoro-olefin.

Since these preliminary experiments indicated that a reaction, probably dimerisation, of chlorotrifluoroethylene was taking place under the influence of heat, a new and improved apparatus was built. Duplicate copper tubes (3′ long × 1″ internal diameter) were mounted in two twin-tube electrical furnaces, each 14″ long, placed end to end, thus enabling gradations of temperature to be achieved. In most of the experiments it was found to be convenient to use the first electric furnace as a preheater at 450—550°, the early experiments having shown that there was little or no reaction at these temperatures. The second furnace provided the reaction zone. The tubes were packed with pre-etched Pyrex glass chips. Experiments were first carried out to establish the optimum reaction temperature; the results are given in Table 1. Because of the complexity of the dimerisation product, complete fractionation was not attempted in these preliminary experiments; instead the fractions, b. p. 50—100°, were treated with zinc dust and ethyl alcohol, to determine the amounts of unsaturated fluorocarbon thus formed (Table 1). The effects of varying the size of the tube packing (Table 2) and of the length of packed section (Table 3) were also investigated. The optimum conditions found for the production of the chlorofluorocarbon intermediate were the use of etched glass chips in a tube graduated from 450—705°, a length of about 14″ being at the latter temperature. Fractionation of the complex pyrolysis product gave few pure compounds. 1 : 2-Dichloro-1 : 2-difluoroethylene and 1 : 1 : 2-trichloro-1 : 2 : 2-trifluoroethane were formed but the chief fraction, b. p. 60°, was a dimer of chlorotrifluoroethylene, later identified as 1 : 2-dichlorohexafluoro*cyclo*butane.

This cyclic chlorofluoro-compound, when refluxed with zinc dust and ethyl alcohol, gave an unsaturated fluorocarbon, b. p. 5—6°, which under ultra-violet irradiation gave a dibromo-addition product. Oxidation of the fluoro-olefin with potassium permanganate solution gave tetrafluorosuccinic acid, m. p. 116°, identified also as the dianilinium salt. By alkaline oxidation of heptafluoroadipic acid (Barbour, Mackenzie, Stacey, and Tatlow, unpublished results) tetrafluorosuccinic acid and its salt were obtained, identical with those

described above. Tetrafluorosuccinic acid has been reported but there is some confusion about the melting point. Henne and Zimmerschied (*J. Amer. Chem. Soc.*, 1947, **69**, 281) reported m. p. 86·4—87·4°, similar values being mentioned by later authors, but Padbury and Kropa (U.S.P. 2,502,478) gave m. p. 116—119°. We found that the acid had m. p. 116° when intensively dried and that it then analysed correctly for the anhydrous acid; if not specially dried the acid had m. p. 87°.

Isolation of tetrafluorosuccinic acid from the oxidation showed that the fluoro-olefin was perfluoro*cyclo*butene, and its precursor the corresponding 1 : 2-dichloro-compound. It was found that this dichlorohexafluoro*cyclo*butane was formed more conveniently from chlorotrifluoroethylene when the latter was heated at about 200° in a rocking autoclave at initial pressures of 50—100 atmospheres. Attempts to polymerise perfluoro*cyclo*butene by aqueous emulsion techniques were unsuccessful, no high-boiling or solid products being formed.

Simultaneously, similar investigations were carried out in the U.S.A. Henne and Ruh (*J. Amer. Chem. Soc.*, 1947, **69**, 279) mentioned briefly the high-pressure dimerisation of chlorotrifluoroethylene to the cyclic dimer, followed by the dechlorination of the latter to perfluoro*cyclo*butene; Harmon (U.S.P. 2,404,374 and 2,436,142) reported a similar series of reactions. The hot-tube reactions of chlorotrifluoroethylene were studied by Miller and his co-workers (*op. cit.*), who used unpacked tubes; below 500° they obtained the cyclic dimer; above 500°, in addition to this, the straight-chain dimer 3 : 4-dichlorohexafluoro-but-1-ene (b. p. 65—66°) and chlorofluoropropenes were formed. We did not isolate a pure fraction corresponding to the straight-chain dimer, but such a product was in fact present. The dechlorinations of the pyrolysis products (b. p. 50—100°) of the preliminary experiments yielded fluoro-olefins containing a small proportion of a more reactive olefin which appeared to be perfluorobutadiene. Small quantities of this diene were isolated in an impure form by dechlorination of the higher-boiling pyrolysis product (b. p. >65°). It appears that formation of the straight-chain dimer is inhibited if the pyrolysis is carried out in glass-packed tubes.

There is now considerable evidence that in fluorinated compounds the *cyclo*butane ring is a fairly stable structure. It is formed quite readily from several fluoro-olefins by self-dimerisation, or by reaction with other olefins [see Coffman, Barrick, Cramer, and Raasch (*J. Amer. Chem. Soc.*, 1949, **71**, 490) for reactions of tetrafluoroethylene in which *cyclo*-butane derivatives are formed].

Experimental

Preparation of Chlorotrifluoroethylene.—Ethyl alcohol (900 c.c.) was stirred in a 2-l. flask fitted with a paddle stirrer and liquid seal, a dropping funnel, and a reflux condenser which was cooled by ice and salt. Zinc dust (540 g.) was slowly added and then, whilst the flask was heated to 70°, 1 : 1 : 2-trichloro-1 : 2 : 2-trifluoroethane (405 g.) was run in during 1½ hours. The crude product which distilled through the cold condenser was redistilled, to give chlorotrifluoro-ethylene (217 g., 86%), b. p. −27°. Booth, Burchfield, *et al.* (*loc. cit.*) gave b. p. −28°.

Pyrolysis of Chlorotrifluoroethylene.—(a) *Apparatus.* The pyrolysis tube was of copper (36″ long × 1″ internal diameter); at the inlet end there was a copper–glass seal to which the vessels containing the chlorotrifluoroethylene were connected through standard ground-glass joints and a glass spiral, whilst at the outlet end a copper–glass ground flange, cooled by a lead spiral through which water was passed, led to a series of traps. The higher-boiling products were condensed in a trap cooled by ice and salt, whilst unchanged chlorotrifluoroethylene was trapped in a vessel cooled by solid carbon dioxide and could then be recycled. A duplicate pyrolysis tube was included alongside the first such that either could be connected to the inlet and the exit train. The pyrolysis tubes were heated by two twin-tube electric furnaces, each 14″ long, arranged end to end so that graded temperatures could be achieved, the temperatures being measured by iron–constantan thermocouples. The pyrolysis tubes were packed with Pyrex glass chips (⅛—¼″) which had been cleaned with chromic acid, etched with potassium fluoride and sulphuric acid, treated a second time with chromic acid, washed with water, and dried. This treatment, together with standardisation of the size of the chips, was necessary to ensure reproducible results.

Chlorotrifluoroethylene was allowed to vaporise at 2·0—2·5 g./min. and was passed through

the pyrolysis tube. The product which did not condense in a trap cooled by ice–salt contained appreciable quantities of unchanged starting material and was recycled until it appeared that no more high-boiling material was produced. Since the product obtained was a very complex mixture it was not completely fractionated in the preliminary experiments, but the material having b. p. 50—100° was treated with zinc dust and ethyl alcohol, and pyrolysis efficiencies were based upon the yield of fluoro-olefin thus obtained.

(b) *Pyrolysis temperature.* The effect of different temperatures are summarised in Table 1. One electric furnace was used as a preheater and maintained the first half of the

TABLE 1.

Temp.	680°	690°	700°	705°	710°	715°	730°	735°	740°	765°
Monomer input (g.)	150	320	310	320	270	300	315	330	345	225
Crude yield, b. p. 50—100° (g.)	16	58	65	70	60	67	70	69	68	39
Yield of derived fluoro-olefin (g.)	0	4·5	8·0	10·0	8·2	7·9	5·5	5·0	4·3	0·8
Yield of derived fluoro-olefin (%)	0	2·0	3·7	4·5	4·4	3·8	2·5	2·2	1·8	0·5

reaction tube at 560° throughout this series, the reaction took place in the second section of the tube, the temperature of which is recorded in the table. The glass catalyst used all passed through an $\frac{1}{8}$″ mesh, and the input rate of chlorotrifluoroethylene was 2·4 g./min. The products were distilled, and material, b. p. 50—100°, was refluxed for 8 hours with a ten-fold excess of zinc dust and ethyl alcohol. No attempt was made to estimate the amounts of unchanged monomer in these experiments, so that the yields of olefin based on the monomer actually consumed were about twice those given.

(c) *Size of tube-packing.* These experiments were carried out with the preheater at 460° and the reaction zone at 705°. Chlorotrifluoroethylene was introduced at 2·4 g./min. The product having b. p. 50—100° (1 part) was refluxed for 8 hours at 85° with zinc dust (2·5 parts) and ethyl alcohol (4 parts) and from this dechlorinated material the fluoro-olefin, b. p. 6—8°, was isolated by fractional distillation. Details are given in Table 2.

TABLE 2.

Size of glass packing	Monomer input (g.)	Unchanged monomer recovered (g.)	Crude yield (g.) of material of b. p.: >20°	Crude yield (g.) of material of b. p.: 50—100°	Yield of olefin (g.)	Yield of olefin (%)
< $\frac{1}{16}$″	262	120	50	39	7·1	7·2
$\frac{1}{16}$—$\frac{1}{8}$″	277	138	92	66	20·0	20·7
$\frac{1}{8}$—$\frac{1}{4}$″	277	124	97	62	10·4	9·8
> $\frac{1}{4}$″	300	126	132	77	8·7	7·2

(d) *Length of packed heated section of tube.* Three experiments were carried out, the tube being packed with catalyst (size $\frac{1}{16}$—$\frac{1}{8}$″) as follows: (i) the tube was packed completely, and the whole length (28″) was heated to 705°, (ii) the tube was packed completely, 14″ was used as a preheater at 405°, the final 14″ being heated to 705°, and (iii) the final 6″ only of the tube was packed with catalyst, the first 14″ of the tube was heated to 405°, the final 14″ being heated to 705°. The monomer input rate was 2·3 g./min. The results are given in Table 3.

TABLE 3.

Expt. no.	Monomer input (g.)	Unchanged monomer recovered (g.)	Crude yield (g.) of material of b. p.: >20°	Crude yield (g.) of material of b. p.: >50°	Yield of olefin (g.)	Yield of olefin (%)
(i)	255	40	110	46	5	3·3
(ii)	270	135	89	62	19	20·2
(iii)	270	—	15	10	0	0

(e) *Fractionation of the crude pyrolysis product.* The crude product, obtained as in experiment (d) (ii), was fractionated in a 3-ft. vacuum-jacketed column packed with Fenske helices. The mixture was complex; after removal of unchanged chlorotrifluoroethylene (b. p. −27°) several fractions of constant b. p. were isolated (yields are expressed as percentages of the amount of unrecovered monomer). Fraction (i) (3·2%), b. p. 22° (Found: *M*, 139. Calc. for $C_2Cl_2F_2$: *M*, 133), was 1 : 2-dichloro-1 : 2-difluoroethylene for which Booth, Burchfield, *et al.* (*loc. cit.*) gave b. p. 21°; fraction (ii) (3·3%), b. p. 43—44° (Found: *M*, 178), was probably dichloro-

tetrafluoropropene; fraction (iii) (6·9%), b. p. 47·5—48·5°, n_D^{19} 1·3578, was 1 : 1 : 2-trichloro-1 : 2 : 2-trifluoroethane (Booth, Mong, and Burchfield, *loc. cit.*, gave b. p. 46·5—47°, n_D^{23} 1·3530); and fraction (iv) (20%), b. p. 59·5—60°, n_D^{14} 1·336 (Found: C, 20·6; Cl, 30·0; F, 49·0%; *M*, 238. Calc. for $C_4Cl_2F_6$: C, 20·6; Cl, 30·4; F, 48·9%; *M*, 233), was 1 : 2-dichlorohexafluoro*cyclo*butane, identical with the material mentioned below.

Fraction (iii) (20·0 g.) was refluxed for 8 hours at 80° with zinc dust (60 g.) and ethyl alcohol (100 c.c.), to give chlorotrifluoroethylene (11·2 g., 90%), b. p. −27°.

High-pressure Dimerisation of Chlorotrifluoroethylene.—The olefin (293 g.) was heated at 220° for 12 hours in a rocking autoclave (initial pressure 80 atm.). From the product, there was isolated, by fractionation as before, 1 : 2-dichlorohexafluoro*cyclo*butane (174 g., 59%), b. p. 58·5—59·5°, n_D^{20} 1·3339, identical with the material from the pyrolysis experiments. Harmon (*loc. cit.*) gave b. p. 58—59°, n_D^{20} 1·3339, and Henne and Ruh (*loc. cit.*), b. p. 59·9°, n_D^{20} 1·3340.

In a reaction at 170—175° for 10 hours the olefin (217 g.) gave the cyclic dimer (21·2 g., 29%; olefin recovered 145 g.) whilst at 180—200° for 12 hours the olefin (338 g.) yielded the cyclic dimer (128 g., 57%; olefin recovered 113 g.).

*Hexafluoro*cyclo*butene.*—1 : 2-Dichlorohexafluoro*cyclo*butane (48·0 g.) was refluxed for 2½ hours with zinc dust (120 g.) and ethyl alcohol (225 c.c.). The product which distilled through the reflux condenser was collected and redistilled, to give perfluoro*cyclo*butene (26·7 g., 80%), b. p. 5—6°, m. p. −59°, d_{-35} 1·60 (Found: *M*, 159. Calc. for C_4F_6: *M*, 162). Harmon (*loc. cit.*) gave b. p. 5—6°, and Henne and Ruh (*loc. cit.*) recorded b. p. 1·1°, m. p. −60·4°.

1 : 2-*Dibromohexafluoro*cyclo*butane.*—The cyclic olefin (10·25 g.) and bromine (5 c.c.) were refluxed for 6 hours in a quartz vessel irradiated by ultra-violet light. The product, after being washed with sodium thiosulphate solution and with water, was dried (P_2O_5), filtered, and distilled, to give 1 : 2-dibromohexafluoro*cyclo*butane (10·6 g., 52%), b. p. 96—97°, n_D^{20} 1·3895 (Found: C, 14·9; F, 35·8%; *M*, 327. Calc. for $C_4Br_2F_6$: C, 14·9; F, 35·4%; *M*, 322). Harmon (*loc. cit.*) reported b. p. 96°, n_D^{20} 1·3889, for this compound.

Tetrafluorosuccinic Acid.—Perfluoro*cyclo*butene (15·7 g.), potassium permanganate (70 g.), and water (300 c.c.) were heated at 105° for 14 hours in a rocking autoclave. The mixture was filtered and the filtrate was decolourised with sulphur dioxide, acidified with concentrated sulphuric acid (50 c.c.), and extracted exhaustively with ether. The ethereal extracts were distilled, and the residue was heated at 75°/15 mm., leaving a very hygroscopic white acidic product (17·1 g., 93%), m. p. 87°.

A part of this acid (8·0 g.) was distilled under diminished pressure; the distillate (7·0 g.), after being dried *in vacuo* over phosphoric oxide for 5 hours at 60°, had m. p. 116—116·5° (Found: C, 25·3; H, 1·4; F, 39·6. Calc. for $C_4H_2O_4F_4$: C, 25·3; H, 1·1; F, 40·0%).

A portion of the acid (1·0 g.) in ether (25 c.c.) was treated with aniline until precipitation was complete. The precipitate, recrystallised from ethyl alcohol–chloroform, was *dianilinium tetrafluorosuccinate* (1·4 g.), m. p. 224° [Found: Equiv., 185 (by titration with standard alkali). $C_{16}H_{16}O_4N_2F_4$ requires Equiv., 188]. The acid and salt are identical with specimens prepared by oxidation of heptafluoroadipic acid (Barbour, Mackenzie, Stacey, and Tatlow, forthcoming publication). For the acid, Henne and Zimmerschied (*loc. cit.*) gave m. p. 86·4—87·4°, and Padbury and Kropa (*loc. cit.*) recorded m. p. 116—119°.

*Attempted Polymerisation of Perfluoro*cyclo*butene.*—This olefin was not polymerised when shaken in sealed tubes for 18 hours at 30—60° in an atmosphere of nitrogen with various aqueous systems including ammonium persulphate–sodium metabisulphite, ammonium persulphate–sodium thiosulphate, and ammonium persulphate–sodium hydroxide, with and without the addition of emulsifying agents. With the alkaline media some hydrolysis occurred with liberation of fluoride ion. The olefin was not affected by prolonged irradiation in ultra-violet light.

The authors are indebted to Imperial Chemical Industries Limited, Dyestuffs Division, Blackley, for the provision of certain materials and facilities.

THE CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

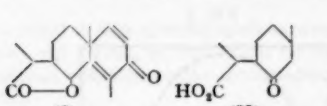
[*Received, June 11th*, 1952.]

734. *Synthesis in the Santonin Series. Part I. Some Oxidation Products of α-(2-Keto-4-methylcyclohexyl)propionic Acid.*

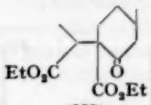
By G. R. Clemo and F. J. McQuillin.

Oxidation of α-(2-keto-4-methyl*cyclo*hexyl)propionic acid (II) by selenium dioxide yields a lactone (IV) having the same chemical properties as the autoxidation product of menthofuran (V) (cf. Treibs, *Ber.* 1937, **70**, 1021; Woodward and Eastman, *J. Amer. Chem. Soc.*, 1950, **72**, 399). Oxidation of α-(3-carboxy-2-keto-4-methyl*cyclo*hexyl)propionic acid (VII; R = H) by nitrous acid and subsequent hydrolysis involve aromatisation, to give the catechol lactone (X); aromatisation is prevented by hydrolysis in the presence of formaldehyde leading to the diketo-acid (IX).

In experiments directed towards the synthesis of santonin (I) and related compounds, the oxidation of α-(2-keto-4-methyl*cyclo*hexyl)propionic acid (II) has been examined with the aim of introducing a hydroxy- or keto-group at position 3.


(I)

(II)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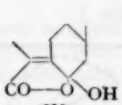
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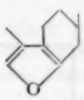

(V)

(VI)

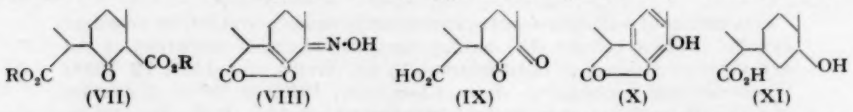
α-(2-Keto-4-methyl*cyclo*hexyl)propionic acid (II), obtained by acid hydrolysis of the keto-dicarboxylic ester (III) (Ruzicka and Steiner, *Helv. Chim. Acta*, 1934, **17**, 614), largely crystallised in one racemic form, m. p. 117°, in good yield. Both the acid and its methyl ester were oxidised only slowly by selenium dioxide in neutral solvents and led to inhomogeneous non-crystalline products. In aqueous acetic acid, however, oxidation of the acid was rapid, leading to a crystalline product, $C_{10}H_{14}O_3$, m. p. 150°, in good yield. This substance, which was readily purified by vacuum-sublimation, was non-ketonic, saturated to bromine in carbon tetrachloride, but attacked fairly rapidly by cold potassium permanganate solution. There was no strong absorption above 220 mμ. Towards alkali the substance behaved as a remarkably stable lactone; although freely soluble in cold aqueous alkali it could not be titrated with alkali nor could its alkaline solution be back-titrated to a definite end-point. On oxidation with alkaline potassium permanganate it gave (±)-2-methyladipic acid in good yield.

These chemical properties coincide closely with those described for the autoxidation product, $C_{10}H_{14}O_3$, m. p. 188°, obtained from menthofuran (V), for which Woodward and Eastman (*J. Amer. Chem. Soc.*, 1950, **72**, 399) proposed structure (IV). Our material in alcoholic alkali showed strong ultra-violet absorption at 265 mμ (log ε 3·93) (cf. Fig. 1), and for the autoxidation product of menthofuran under similar conditions Woodward and Eastman found $\lambda_{max.}$ 265 mμ (log ε 3·72). Also, in agreement with these authors, our material was found to undergo ready dehydration to a product $C_{10}H_{12}O_2$ on distillation from potassium hydrogen sulphate. This showed the strong absorption [$\lambda_{max.}$ 276 mμ (log ε 4·14)] expected of the conjugated system present in (VI). For patulin, which contains essentially the same chromophore as (VI), Bergel, Morrison, Moss, and Rindeknecht (*J.*, 1944, 417) give $\lambda_{max.}$ 276·5 mμ (log ε 4·22); for deoxypatulin, Woodward and Singh (*J. Amer. Chem. Soc.*, 1949, **71**, 758) give $\lambda_{max.}$ 273 mμ (log ε 4·17).

The rapid oxidation of (II) in aqueous acetic acid is clearly due to acid-catalysed enolisation and oxidation of the enolic lactone form at the "allyl" 1'-position, which is further activated by the adjacent carbonyl group. Concomitant acid-catalysed oxotropic rearrangement leads to (IV) which also is the only structure consistent with the ultra-violet absorption and chemical properties.

This result may be taken as synthetical verification of the structure of the menthofuran autoxidation product, the difference in melting point being due to our material being a racemic mixture.

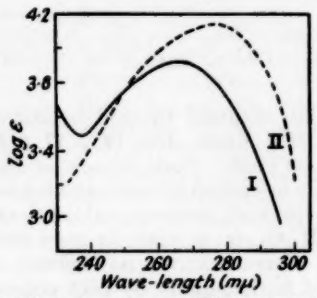
In view of this behaviour of α-(2-keto-4-methyl*cyclo*hexyl)propionic acid, the carbethoxy-derivative (VII) (R = Et) was prepared, so as to facilitate oxidation at the activated position 3. This was readily obtained by alcoholysis of the intermediate (III) and re-cyclisation. In an analogous case Openshaw and Robinson (*J.*, 1937, 941; 1946, 912) were able to effect a rearrangement of this type in one operation by means of alcoholic



sodium ethoxide. In our case these conditions led to much high-boiling material, and isolation of the intermediate triethyl 2-methylheptane-1 : 5 : 6-tricarboxylate was found to be necessary. Acid hydrolysis of the recyclised product gave the same keto-acid (II), m. p. 117°, as was obtained directly from (III).

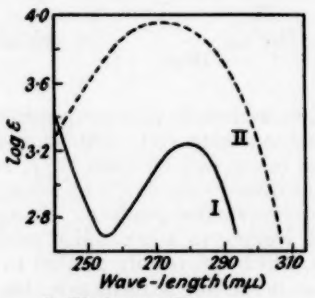
Oxidation was effected by treatment of the corresponding dicarboxylic acid (VII; R = H) with nitrous acid (cf. Kötz and Wunstorf, *J. pr. Chem.*, 1913, **88**, 528; Kötz, Nussbaum, and Takens, *ibid.*, 1914, **90**, 378), leading to a product $C_{10}H_{13}O_3N$ regarded as the oximino-

FIG. 1.



I, *The hydroxy-lactone* (IV) *in alcoholic potassium hydroxide.*
II, *The unsaturated lactone* (VI).

FIG. 2.



I, *The lactone* (X).
II, *The diketo-acid* (IX).

enol-lactone (VIII) or the related oximino-αβ-butenolide. This material which was soluble in caustic alkali, but insoluble in sodium hydrogen carbonate solution, gave a characteristic green colour with alcoholic ferric chloride. Acid hydrolysis of the oximino-lactone afforded as main product a crystalline lactone, m. p. 107°, showing no ferric chloride colour when pure, but an intense green colour when freshly liberated from its alkaline solution. Its alkaline solution rapidly became deep red, this commencing at the air interface. The substance gave no carbonyl derivative. It was saturated to bromine in carbon tetrachloride and with bromine in acetic acid gave a red derivative decolorised by sulphurous acid, which is typical of *o*-quinone formation. These reactions were clearly not those of the diketone (IX) to be expected from simple hydrolysis of (VIII), nor of a derived enol lactone. Analyses indicated a formula, $C_{10}H_{10}O_3$, corresponding to the catechol derivative (X), and the substance was found to couple with diazotised *p*-nitroaniline. The catechol structure was supported by the ultra-violet absorption [$\lambda_{max.}$ 279 mμ (log ε 3·23) (cf. Fig. 2)]. For catechol Morton and Stubbs (*J.*, 1940, 1347) found $\lambda_{max.}$ 278 mμ (log ε 3·42), and closely similar figures are given for a number of catechol derivatives (Adams, Cain, and Wolff, *J. Amer. Chem. Soc.*, 1940, **62**, 732). Corresponding α-diketones in general absorb at somewhat shorter wave-lengths, but are characterised more particularly by extinction values of the order of log $\varepsilon_{max.}$ 4. For diosphenol, Gillam, Lynas-Gray, Penfold, and Simonsen (*J.*, 1941, 62) found $\lambda_{max.}$ 274 mμ (log ε 4·04). In the sterol series, for a 2 : 3-dione Rosenheim and Steiner (*J.*, 1938, 353) found $\lambda_{max.}$ 270 mμ (log ε 3·70 and 3·93 for isomeric forms); for a 6 : 7-diketo-sterol Heilbron, Jones, and Spring (*J.*, 1937, 801) found $\lambda_{max.}$ 274·5 mμ (log ε 4·03).

The substance $C_{10}H_{10}O_3$, m. p. 107°, was not hydrogenated over palladised charcoal in alcohol, but in presence of Adams's platinum oxide in acetic acid rather more than four molecular equivalents of hydrogen were absorbed, to give a hydroxy-acid, $C_{10}H_{18}O_3$, which is unchanged on distillation and therefore regarded as the δ-hydroxy-acid (XI). The hydrogen uptake is consistent only with the catechol structure (X), and hydrogenolysis of the lactone ring provides an example in the aromatic series of the behaviour of βγ-butenolides noted by Jacobs and Scott (*J. Biol. Chem.*, 1930, **87**, 601).

In the formation of (X), aromatisation apparently occurs through oxidation during hydrolysis of the oximino-lactone. By hydrolysis in the presence of formaldehyde (cf. Kötz, Nussbaum, and Takens, *loc. cit.*) it was possible to obtain a substance, $C_{10}H_{14}O_4$, m. p. 155—156°, corresponding to the diketone (IX), but not in good yield. This substance which also showed a deep green colour reaction with alcoholic ferric chloride, gave, however, a stable yellow solution in alkali. The ultra-violet absorption (cf. Fig. 2) showed the expected maximum at 272 mμ (log ε 3·95) in agreement with the data noted above.

In view of the structural analogy between (VI) and patulin, this substance was tested but found to have no antibiotic activity; (III) and (VII) were similarly inactive.

Experimental

Ethyl 2-Keto-4-methylcyclohexanecarboxylate.—This was obtained, with b. p. 127—128°/17 mm., n_D^{18} 1·4763, in 60% yield by the general method of *Org. Synth.*, Coll. Vol. II, p. 532, but without isolation of the intermediate glyoxylic ester (cf. Kötz and Hesse, *Annalen*, 1905, **342**, 321).

Diethyl α-(1-Carboxy-2-keto-4-methylcyclohexyl)propionate.—This ester was obtained, with b. p. 105°/0·1 mm., n_D^{18} 1·4737, in 55% yield from ethyl 2-keto-4-methyl*cyclo*hexanecarboxylate with an equivalent of ethyl α-bromopropionate in dry ethyl-alcoholic sodium ethoxide (Ruzicka and Steiner, *Helv. Chim. Acta*, 1934, **17**, 614).

Hydrolysis of Diethyl α-(1-Carboxy-2-keto-4-methylcyclohexyl)propionate.—(i) Gentle refluxing with concentrated hydrochloric acid for 2 hours gave as the main acid product a viscous colourless oil, b. p. 135—140°/0·04 mm., n_D^{19} 1·4778, corresponding to *α-(1-carbethoxy-2-keto-4-methylcyclohexyl)propionic acid* (Found: C, 61·2; H, 8·1. $C_{13}H_{20}O_5$ requires C, 61·0; H, 7·8%).

(ii) Hydrolysis of the diethyl ester (6·9 g.) in glacial acetic acid (25 c.c.) with concentrated hydrochloric acid (25 c.c.) on the steam-bath for 6 hours afforded *α-(2-keto-4-methylcyclohexyl)propionic acid*, b. p. 145—150°/0·1 mm. (2·2 g.), which largely crystallised. Separation of the crystalline material by means of benzene–light petroleum (b. p. 40—60°) gave, after recrystallisation from the same solvent, *α-(2-keto-4-methylcyclohexyl)propionic acid*, m. p. 117°, as rosettes of fine prisms (Found: C, 65·1; H, 8·9. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%). The *2 : 4-dinitrophenylhydrazone* formed orange yellow prisms, m. p. 219°, from ethyl alcohol–ethyl acetate (Found: C, 53·0; H, 5·7. $C_{16}H_{20}O_6N_4$ requires C, 52·7; H, 5·4%).

Oxidation of α-(2-Keto-4-methylcyclohexyl)propionic Acid with Selenium Dioxide.—α-(2-Keto-4-methyl*cyclo*hexyl)propionic acid (9·2 g.) and selenium dioxide (5·6 g.) in acetic acid (40 c.c.) and water (5 c.c.) were heated under reflux for 2 hours. Removal of precipitated selenium, and of solvent, gave a brown viscous oil which was taken into warm sodium carbonate solution. Acidification gave a brown solid (5·5 g.) which was recrystallised from benzene–light petroleum and further purified by vacuum-sublimation at 100—110°/0·1 mm., to give the colourless *lactone*, m. p. 150°, of α-(2 : 2-dihydroxy-4-methyl*cyclo*hexylidene)propionic acid (Found: C, 66·2; H, 8·0. $C_{10}H_{14}O_3$ requires C, 66·0; H, 7·7%), insoluble in aqueous sodium carbonate solution in the cold, slowly soluble on warming, but rapidly soluble in sodium hydroxide solution.

Further oxidation. This lactone (0·4 g.) in sodium hydroxide solution (15 c.c. of 6%) was oxidised with potassium permanganate (1 g.) in water (75 c.c.), and the solution then treated with sulphur dioxide and concentrated *in vacuo*. The residue, acidified and thoroughly extracted with ether, gave a viscous oil (0·4 g.) which largely crystallised. The crystals, separated by means of ether–light petroleum, were purified by vacuum-sublimation and obtained as a colourless crystalline powder, m. p. 89° undepressed on admixture with authentic (±)-2-methyladipic acid.

Dehydration. α-(2 : 2′-Dihydroxy-4-methyl*cyclo*hexylidene)propionic lactone (0·3 g.) with a few crystals of potassium hydrogen sulphate was gently refluxed for a few minutes in a partial vacuum and then twice distilled, to give a colourless mobile oil, b. p. 90°/0·01 mm., d_D^{17} 1·5471 (Found: C, 72·8; H, 7·6. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·3%), this being the *lactone* (VI) of α-(2-hydroxy-4-methyl*cyclo*hex-2-enyl)propionic acid.

Triethyl 2-Methylheptane-1 : 5 : 6-tricarboxylate.—Diethyl α-(1-carboxy-2-keto-4-methyl*cyclo*hexyl)propionate (22·8 g.) in dry alcohol (15 c.c.) was added to a solution of sodium ethoxide [from sodium (1·8 g.) in dry alcohol (40 c.c.)], cooled in ice. After 3 days under nitrogen, the solution was treated with ice and acidified with dilute hydrochloric acid, the liberated oil taken into ether, and the solution washed with water and dried. Distillation afforded a small fraction, b. p. 80—100°/0·4 mm., showing a red-violet ferric chloride colour, and a main fraction (13·3 g.), b. p. 135—145°/0·3 mm., n_D^{22} 1·4463; of *triethyl 2-methylheptane-1 : 5 : 6-tricarboxylate* (Found: C, 61·7; H, 9·4. $C_{17}H_{30}O_6$ requires C, 61·8; H, 9·1%).

*Diethyl α-(3-Carboxy-2-keto-4-methyl*cyclo*hexyl)propionate.*—Sodium powder (1·4 g.) under benzene (35 c.c.) was treated with trimethyl 2-methylheptane-1 : 5 : 6-tricarboxylate (20 g.) in benzene (30 c.c.) and a little dry alcohol, and reaction completed on the steam-bath during 3½ hours. After being kept overnight the reaction mixture was treated with ice-water and acidified with dilute acetic acid, and the benzene solution was separated. The aqueous layer was re-extracted and the combined extracts were dried and distilled, giving a main fraction (9·8 g.), b. p. 131—137°/0·4 mm., n_D^{21} 1·4618, of *diethyl α-(3-carboxy-2-keto-4-methyl*cyclo*hexyl)-propionate*, giving a red-violet ferric chloride colour (Found: C, 63·1; H, 8·8. $C_{15}H_{24}O_5$ requires C, 63·3; H, 8·5%).

Hydrolysis of this ester (2·5 g.) in glacial acetic acid (5 c.c.) with concentrated hydrochloric acid (15 c.c.) on the steam-bath for 6 hours afforded α-(2-keto-4-methyl*cyclo*hexyl)propionic acid (1·2 g.), b. p. 140—150°/0·1 mm., from which the crystalline acid, m. p. 117°, was obtained in good yield.

*Reaction of α-(3-Carboxy-2-keto-4-methyl*cyclo*hexyl)propionic Acid with Nitrous Acid.*—Diethyl α-(3-carboxy-2-keto-4-methyl*cyclo*hexyl)propionate (5·65 g.) was shaken mechanically with a cold solution of potassium hydroxide (2·5 g.) and sodium nitrite (1·4 g.) in water (57 c.c.) for 24 hours. A small amount of oil was then removed by ether, and the yellow aqueous layer separated and cooled to 0°. Concentrated sulphuric acid (1·5 c.c.) was then added dropwise with stirring during 15 minutes. After some hours the liquid was thoroughly extracted with ether, to yield, after drying and removal of solvent, 4·7 g. of red-brown oil (A). On attempted distillation this partly decomposed, but a fraction could be collected, having b. p. 120—125°/0·05 mm. and giving analytical figures corresponding to *α-(2-hydroxy-4-methyl-3-oximino*cyclo*hex-1-enyl)propionic lactone* ((Found: C, 61·7; H, 7·1; N, 7·4. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·7; N, 7·2%). This was a viscous oil showing a dark green ferric chloride colour reaction in alcohol. It was insoluble in sodium hydrogen carbonate solution, but soluble in warm sodium hydroxide solution.

Hydrolysis. The above crude material (A) (19 g.) was heated with acetic acid (25 c.c.), concentrated hydrochloric acid (40 c.c.), and water (80 c.c.) on the steam-bath for 2 hours. It was then diluted somewhat, cooled, saturated with ammonium sulphate, and extracted thoroughly with ether. Distillation of the recovered oil gave material (6·6 g.), b. p. 130—170°/0·5 mm. This was separated by means of sodium hydrogen carbonate solution into an acid fraction [isolated as a colourless crystalline solid, m. p. 117° (3 g.) after distillation and recrystallisation from light petroleum (b. p. 40—60°)], and a neutral fraction. The latter on distillation gave material (1·7 g.), b. p. 115—120°/0·2 mm., which crystallised at once and was obtained as colourless prisms, m. p. 107°, by recrystallisation from light petroleum (b. p. 40—60°). The acid fraction gave no m. p. depression on admixture with α-(2-keto-4-methyl*cyclo*hexyl)propionic acid. The neutral material *2 : 3-dihydro-7-hydroxy-2-keto-3 : 6-dimethylbenzofuran*, which could also be very conveniently purified by vacuum-sublimation (80—90°/0·2 mm.) (Found: C, 67·2; H, 5·6. $C_{10}H_{10}O_3$ requires C, 67·3; H, 5·7%), was insoluble in sodium hydrogen carbonate solution, but in strong alkali it at once gave a solution which rapidly developed a bright red colour at the air interface. It showed no colour with ferric chloride in alcohol, but when it was liberated into ether from its alkaline solution the ethereal solution gave with alcoholic ferric chloride an intense green colour. It gave no carbonyl derivatives.

On hydrogenation in glacial acetic acid with Adams's platinum oxide rather more than four mols. of hydrogen were rapidly absorbed by the benzofuran without a break in the rate curve. The resultant *α-(3-hydroxy-4-methyl*cyclo*hexyl)propionic acid* formed a gum, b. p. 145°/0·02 mm. (Found: C, 64·7; H, 10·0. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·7%).

The crude material (A) (5·65 g.) was stirred vigorously with 30% aqueous formaldehyde (15 c.c.) and treated gradually with concentrated hydrochloric acid (10 c.c.). After 1½ hours the solution was neutralised with aqueous ammonia and extracted with ether, yielding a brown oil (1·6 g.) which partly crystallised. Separation of the solid by means of benzene–light petroleum (b. p. 40—60°) and recrystallisation from the same solvents gave *α-(2 : 3-diketo-4-*

methylcyclohexyl)propionic acid, m. p. 155—156° (Found: C, 60·3; H, 7·3. $C_{16}H_4O_4$ requires C, 60·6; H, 7·2%).

The authors are grateful to Dr. J. G. P. Hutchinson, Royal Victoria Infirmary, Newcastle-on-Tyne, for the biological tests. One of them (F. J. McQ.) is indebted to the University of Durham for the award of an Imperial Chemical Industries Research Fellowship during tenure of which part of this work was carried out.

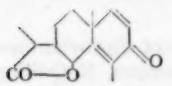
KING'S COLLEGE, NEWCASTLE-ON-TYNE, 1. [*Received, May 21st*, 1952.]

735. *Synthesis in the Santonin Series. Part II.**

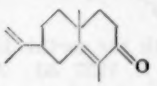
By G. R. CLEMO and F. J. MCQUILLIN.

(−)-Dihydrocarvone (VI) has been converted *via* an epoxide (VII) into a (−)-α-(3-keto-4-methyl*cyclo*hexyl)propionic acid (IX) from which the keto-esters (XII) and (XIV) related to santonin have been obtained. The bromination and dehydrobromination of (XII) have been examined and the nature of the products is discussed.

(−)-SANTONIN (I) and the related lactones occurring in *Artemesia* species, and the alantolactones of *Inula Helenium*, represent in the sesquiterpene group the type of terpenoid substance in which one carbon atom of the terminal isoprene unit occurs as a carboxyl group or its equivalent. These lactones possess the selinene–eudesmol molecular skeleton, and in the location of unsaturation and of the keto-group of santonin there is a striking formal resemblance between, for example, santonin (I) and α-cyperone (II), and



(I)



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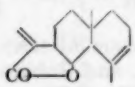

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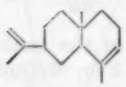

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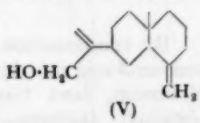
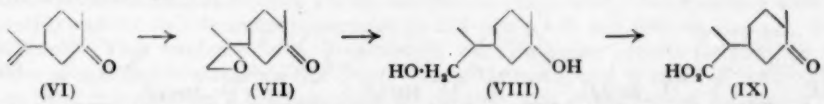


(V)

also between alantolactone (III) and α-selinene (IV). This resemblance is sufficiently close to suggest an underlying biogenetic relationship through a common precursor in which the carboxyl group of the lactones occurs as an alcohol group. A structure of this type is represented in Nature by the sesquiterpene alcohol sesquibenihiol (V), whilst a similar terminal alcohol group occurs also in the santalols and in lanceol. On this view it may be significant that costus root oil contains a series of sesquiterpene lactones, and a related primary alcohol, costol $C_{15}H_{24}O$, although the structures of these substances have not been fully elucidated (Semmler and Feldstein, *Ber.*, 1914, **47**, 2433; Naves, *Helv. Chim. Acta*, 1948, **31**, 1172).

These speculations suggested that in an approach to the synthesis of santonin it would be of interest to attempt the oxidation of the terminal isoprene unit of a simpler terpene. With this purpose (−)-dihydrocarvone (VI) has been oxidised at the terminal double bond by means of the sequence :



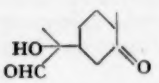
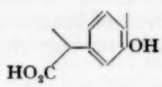
(VI) (VII) (VIII) (IX)

and in this way a keto-acid (IX) has been obtained which offers a convenient intermediate for the synthesis of substances related to santonin. (−)-Dihydrocarvone reacted rapidly and exothermally with perbenzoic acid in chloroform, to give a lævorotatory saturated neutral ketonic product, $C_{10}H_{16}O_2$, corresponding with the epoxide (VII). This was accompanied in smaller amount by a higher-boiling ketone, $C_{10}H_{18}O_3$, regarded as the corresponding glycol. The epoxide could be characterised by means of a semicarbazone. With 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid, however, a bis-2 : 4-dinitrophenylhydrazone, $C_{22}H_{24}O_9N_8$, was obtained, which is most simply regarded as corresponding with the hydroxy-keto-aldehyde (X) formed by fission of the epoxide followed by

* Part I, preceding paper.

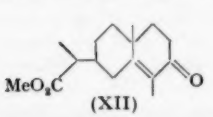
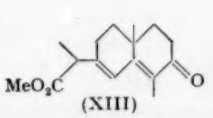
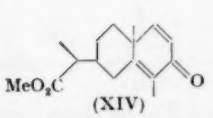
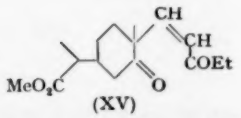
oxidation, as in a case recently reported by Braude and Forbes (*J.*, 1951, 1762). In the preparation of the epoxide no evidence was obtained of oxidative ring fission of the type noted by Bayer and Villiger (*Ber.*, 1900, **33**, 1569) and studied more recently by Friess (*J. Amer. Chem. Soc.*, 1949, **71**, 2571). The rate of reaction of perbenzoic acid with dihydrocarvone in moist chloroform at 0°, followed roughly by titration, indicated a bimolecular velocity constant of *ca.* 5×10^{-4} l. mol.$^{-1}$ sec.$^{-1}$, in good agreement with a value of $5{\cdot}8 \times 10^{-4}$ found by Meerwein, Ogait, Prang, and Serini (*J. pr. chem.*, 1926, **113**, 9) for *p*-menth-8(9)-ene-1 : 2-diol under similar conditions. For the oxidative fission of *cyclo*hexanone Friess (*loc. cit.*) found a similar rate at 26·98° and it is clear that reaction at the olefinic centre occurs the more readily.

In the hydrogenolysis of 1 : 2-epoxydecane, Newman, Underhill, and Renoll (*J. Amer. Chem. Soc.*, 1949, **71**, 3362) have indicated that reduction to the primary alcohol is favoured by the use of Raney nickel catalyst under neutral conditions. With Raney nickel in alcohol the epoxide (VI) was converted into a glycol, $C_{10}H_{16}O_2$ which could be oxidised in moderate yield to a lævorotatory keto-acid, $C_{10}H_{16}O_3$. The derived methyl ester of this keto-acid was readily dehydrogenated with palladised charcoal to a phenolic carboxylic acid, $C_{10}H_{12}O_3$, characterised as a hydrate and a monophenylazo-derivative. These results clearly indicate that the glycol formed on hydrogenation of the epoxide consists largely of the 2 : 9-diol (VIII), leading to the keto-acid (IX) and to a dehydrogenated phenolic acid (XI).

(X)   (XI)

By condensation of the methyl ester of (IX) with the methiodide of diethylaminopentan-3-one (cf. du Feu, McQuillin, and Robinson, *J.*, 1937, 53; Adamson, McQuillin, Robinson, and Simonsen, *J.*, 1937, 1576) a bicyclic keto-ester, $C_{16}H_{26}O_3$, was obtained, showing the characteristic absorption of an αβ-unsaturated ketone [$\lambda_{max.}$ 245 mμ (log ε 4·05)]. This condensation was conveniently effected by means of sodiotriphenylmethane in ether and the products were separated from triphenylmethane by alkaline hydrolysis which served also to complete the ring closure of the intermediate diketo-ester.

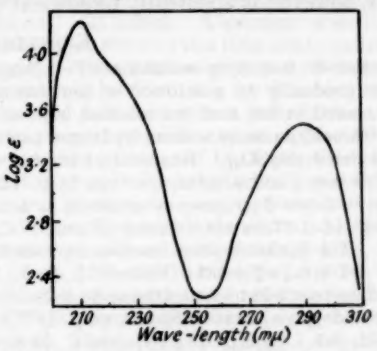
The bicyclic keto-ester in the presence of palladised charcoal absorbed one molecular proportion of hydrogen and in the presence of Adams's platinum oxide in acetic acid two molecular equivalents. The product of the latter reaction, after hydrolysis and dehydrogenation with selenium, gave 7-ethyl-1-methylnaphthalene; the picrate of this was readily purified and no significant amount of a second hydrocarbon was formed. The keto-ester is therefore regarded as being (XII). It was found to be dextrorotatory, in agreement with the formation of (+)-α-cyperone in the analogous condensation of diethylaminopentan-3-one methiodide with (−)-dihydrocarvone (Adamson, McQuillin, Robinson, and Simonsen, *loc. cit.*).

 (XII)  (XIII)  (XIV)  (XV)

With the object of obtaining the diunsaturated keto-ester (XIV) more closely related to santonin, methyl α-(3-keto-4-methyl*cyclo*hexyl)propionate was condensed with ethyl ethynyl ketone in the presence of sodiotriphenylmethane in ether (cf. Woodward and Singh, *J. Amer. Chem. Soc.*, 1950, **72**, 494). This gave a product $C_{16}H_{22}O_3$ showing $\lambda_{max.}$ 240 mμ (log ε 3·96), which is in general agreement with a structure (XIV), but the yield was inconveniently small. There is more side reaction than in the Mannich-base condensation, and also if a Michael addition to the ethynyl group is regarded as the first step in the condensation it is clear that only a *cis*-form of an intermediate (XV) is likely to undergo cyclodehydration. In an analogous condensation between 2-methyl*cyclo*hexanone and

methyl propiolate Bachmann and Raunio (*ibid.*, p. 2530, 2533) observed predominantly anionoid attack by the ethynyl group on the keto-group rather than Michael addition, and this type of reaction may compete in the present case.

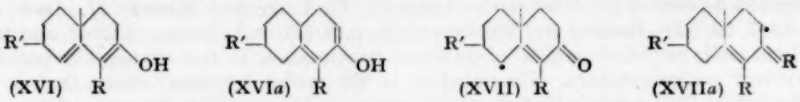
Bromination of (XII) was therefore examined with a view to introducing the required second double bond by dehydrobromination. In the analogous case of 3-keto-$\Delta^{4(5)}$-steroids Meystre and Wettstein (*Experientia*, 1946, **2**, 408) observed bromination in the conjugated 6-position by *N*-bromosuccinimide. La Forge and Soloway (*J. Amer. Chem. Soc.*, 1947, **69**, 979), Dauben and Wenkert (*ibid.*, p. 2074), and Crombie, Elliott, and Harper (*J.*, 1950, 971) reported similar preferential bromination in the conjugated position of substituted *cyclo*pentenones. Examination of the model, however, shows that in (XII) the 8-position is to some extent sterically hindered, thus possibly favouring bromination in position 3. Treatment of (XII) with one molecular proportion of *N*-bromosuccinimide in carbon tetrachloride in the presence of benzoyl peroxide and dehydrobromination of the product by means of boiling collidine gave a product showing double absorption maxima in the ultra-violet [$\lambda_{max.}$ 245 (log ε 3·82) and 294 mμ (log ε 3·65)], the second corresponding



clearly with the conjugated diunsaturated keto-ester (XIII), and the former with the isomer (XIV) or with the keto-ester (XII) which cannot be very different in their light absorption. Chromatography on alumina gave a first fraction showing $\lambda_{max.}$ 247 mμ (log ε 4·13) and absorbing almost exactly one molecular equivalent of hydrogen in the presence of palladised charcoal; later fractions showed increasing intensity of absorption at 294 mμ and increased uptake of hydrogen and corresponded with the starting material (XII) plus increasing proportions of the diunsaturated keto-ester (XIII). A more strongly absorbed still later fraction, however, showed again a single strong absorption maximum [λ 242 mμ (log ε 3·89)], and took up almost two equivalents of hydrogen in the presence of palladised charcoal, giving a ketonic product. These properties correspond with a dienone structure (XIV), and after digestion with fuming hydrochloric acid at 35° this material had absorption maxima at 212 (log ε 3·98) and 290 mμ (log ε 3·32), corresponding with the maxima shown by (±)-desmotroposantonin [λ 212 (log ε 4·2) and 290 mμ (log $\varepsilon_{max.}$ 3·47) (cf. Figure). This evidence of a desmotropic rearrangement clearly established the presence of material of structure (XIV) (cf. Clemo, Haworth, and Walton, *J.*, 1929, 2368) and on careful distillation a fraction could be isolated, and characterised by means of a semicarbazone, corresponding with (XIV) and showing a single absorption maximum at 272 mμ (log ε 4·17) in agreement with this structure.

In the bromination of (XII) by means of *N*-bromosuccinimide free bromine was observed from an early stage. The solution remained yellow-orange until the whole of the imide had reacted and then began to darken. At this stage hydrogen bromide could be detected. Bromine, liberated through the release of hydrogen bromide from an intermediate bromo-ketone, may therefore be the principal reagent in this case, the solution being buffered to low acidity so long as *N*-bromosuccinimide remains. The reaction appeared to be catalysed by benzoyl peroxide, but this may also be effective in part through the formation of acidic products. There is evidence for similar intervention of bromine

and the formation of addition products as a concomitant to allylic bromination of an olefin (Wieland and Miescher, *Helv. Chim. Acta*, 1947, **30**, 1876). In the monobromination of 3-keto-$\Delta^{4(5)}$-steroids by bromine or *N*-bromosuccinimide, substitution takes place primarily in the 6-position (cf. Djerassi *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 4534), and it is to be expected that the factors stabilising an enol (XVI; R = R′ = H) in comparison with (XVI*a*; R = R′ = H) will be effective in a similar stabilisation of an intermediate



radical (XVII; R = R′ = H) in comparison with (XVII*a*; R = R′ = H). In (XII), however, where R = Me and R′ = CHMe·CO_2Me, removal of a hydrogen atom or a proton which is the rate-determining step is hindered at position 8 whereas at position 3 one hydrogen atom lies " equatorially " away from the substituent at $C_{(10)}$ and is unhindered. The effect, however, is apparently insufficient to prevent considerable bromination at $C_{(8)}$.

Experimental

(−)-2-*Keto*-8 : 9-*epoxy*-p-*menthane*.—(−)-Dihydrocarvone (24 g.) in chloroform (50 c.c.) was added gradually to a solution of perbenzoic acid (22·25 g., 1·02 equivs.) in chloroform (550 c.c.) cooled in ice, and the solution kept at 0° for 24 hours. The liquid was thoroughly washed with cold aqueous sodium hydrogen carbonate (to remove benzoic acid) and then with water and dried ($MgSO_4$). Removal of solvent and distillation gave material (18·3 g.), b. p. 135—145°/9 mm., and a small fraction, b. p. 120—125°/0·1 mm. Redistillation of the main fraction gave 2-*keto*-8 : 9-*epoxy*-p-*menthane* as a colourless liquid, b. p. 65°/0·1 mm., n_D^{20} 1·4751, $[\alpha]_D$ −13·2° (*c*, 1·27 in chloroform) (Found : C, 71·1; H, 9·8. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·5%). The higher-boiling fraction on redistillation afforded a colourless viscous oil, b. p. 120—125°/0·1 mm., n_D^{20} 1·4841 (Found : C, 64·9; H, 9·2. $C_{10}H_8O_3$ requires C, 64·5; H, 9·5%), corresponding to a 2-keto-*p*-menthane-8 : 9-diol (cf. Wallach, *Ber.*, 1895, **28**, 2706).

The epoxide gave a *semicarbazone*, m. p. 187°, colourless prisms from methyl alcohol (Found : C, 58·3; H, 8·5. $C_{11}H_{19}O_2N_3$ requires C, 58·6; H, 8·4%). 2 : 4-Dinitrophenylhydrazine in alcoholic sulphuric acid gave orange-yellow prisms, m. p. 205°, from ethyl alcohol–ethyl acetate, corresponding with 2-(3-*keto*-4-*methyl*cyclo*hexyl*)*lactaldehyde bis*-2 : 4-*dinitrophenylhydrazone* (Found : C, 48·7; H, 4·3. $C_{22}H_{24}O_9N_8$ requires C, 48·6; H, 4·4%).

p-*Menthane*-2 : 9-*diol*.—Dihydrocarvone epoxide (18 g.) in ethyl alcohol (120 c.c.) with Raney nickel (*ca.* 10 g.) was hydrogenated at 100°/90 atm. for 3 hours. Recovery of the material and distillation gave material (4·3 g.), b. p. 75—80°/0·5 mm., and (10·2 g.) b. p. 115—125°/0·4 mm. The first fraction was redistilled and *p*-menthol obtained as a mobile oil, b. p. 45°/0·2 mm., n_D^{20} 1·4677 (Found : C, 76·8; H, 12·7. Calc. for $C_{10}H_{20}O$: C, 76·9; H, 12·8%). The main fraction was redistilled and afforded p-*menthane*-2 : 9-*diol* as a viscous oil, b. p. 115—117°/0·4 mm., n_D^{19} 1·4922, $[\alpha]_D$ −14·1° (*c*, 1·2 in chloroform) (Found : C, 69·8; H, 11·9. $C_{10}H_{20}O_2$ requires C, 69·8; H, 11·6%).

α-(3-*Keto*-4-*methyl*cyclo*hexyl*)*propionic Acid*.—*p*-Menthane-2 : 9-diol (9 g.) in acetone (100 c.c) was treated gradually, with stirring, with chromic acid (11 g.) in water (50 c.c.) and concentrated sulphuric acid (5 c.c.), the temperature being kept at 25—30°. After 8 hours at room temperature, the mixture was somewhat diluted with water and thoroughly extracted with ether, ammonium sulphate being added to assist separation. α-(3-*Keto*-4-*methyl*cyclo*hexyl*)-*propionic acid*, separated by means of sodium hydrogen carbonate solution, was a viscous oil, b. p. 125—130°/0·05 mm. (Found : C, 65·2; H, 9·1. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%). The 2 : 4-*dinitrophenylhydrazone* formed orange prisms, m. p. 168°, from benzene–light petroleum (Found : C, 53·0; H, 5·7. $C_{16}H_{20}O_6N_4$ requires C, 52·75; H, 5·5%). The *methyl* ester, obtained by methyl-alcoholic sulphuric acid, had b. p. 73°/0·1 mm., n_D^{19} 1·4664, $[\alpha]_D$ −10·3° (*c*, 2·8 in chloroform) (Found : C, 66·7; H, 9·5. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·1%).

The neutral fraction from this oxidation on distillation gave some recovered menthanediol and a fraction, b. p. 75—80°/0·1 mm., n_D^{20} 1·4709, reducing Schiff's and Fehling's reagents and yielding 2-(3-*keto*-4-*methyl*cyclo*hexyl*)*propaldehyde bis*-2 : 4-*dinitrophenylhydrazone*, m. p. 231°, as orange prisms from ethyl acetate (Found : C, 49·7; H, 4·7%. $C_{22}H_{24}O_8N_8$ requires C, 50·0; H, 4·6%).

Dehydrogenation of Methyl α-(3-*Keto*-4-*methyl*cyclo*hexyl*)*propionate*.—Methyl α-(3-keto-4-

methyl*cyclo*hexyl)propionate (1 g.) was heated with palladised charcoal (0·4 g.) for 3 hours at 285°. α-(3-*Hydroxy*-4-*methylphenyl*)*propionic acid*, isolated by aqueous sodium hydrogen carbonate, was distilled and obtained as a colourless glass, b. p. 150°/0·1 mm., which crystallised in air. This *hydrate* crystallised from benzene–light petroleum (b. p. 60—80°) as colourless prisms, m. p. 47° (Found: C, 60·6; H, 7·4. $C_{10}H_{12}O_3,H_2O$ requires C, 60·6; H, 7·1%). When kept over phosphoric oxide it reverted to a colourless glass. Dehydration was completed *in vacuo* at 100° (Found: C, 66·3; H, 7·0. $C_{10}H_{12}O_3$ requires C, 66·6; H, 6·7%). The acid coupled with benzenediazonium chloride, giving a *phenylazo*-derivative, orange yellow prisms, m. p. 144°, from benzene–light petroleum (Found: C, 67·6; H, 6·0. $C_{16}H_{16}O_3N_2$ requires C, 67·6; H, 5·7%).

Methyl α-(1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-7-*keto*-8 : 10-*dimethyl*-2-*naphthyl*)*propionate*.—1-Diethylaminopentan-3-one (Adamson, McQuillin, Simonsen, and Robinson, *J.*, 1937, 1576) gave a *methiodide*, m. p. 70—71°, as prisms from acetone (Found: C, 40·5; H, 7·4. $C_{10}H_{22}ONI$ requires C, 40·2; H, 7·4%).

1-Diethylaminopentan-3-one (6·8 g.) was treated gradually with cooling with methyl iodide (6·2 g.) so that the crystalline methiodide was deposited over the walls of the flask (cf. Cornforth and Robinson, *J.*, 1949, 1855), and a solution of methyl α-(3-keto-4-methyl-*cyclo*hexyl)propionate (8·5 g.) in dry ether (85 c.c.) was added. A solution of sodiotriphenylmethane (from triphenylmethyl chloride, 16 g., in ether, 370 c.c.) was then run in under nitrogen, the red colour being almost instantly discharged. After 3 hours at 0° and 36 hours at room temperature under nitrogen the mixture was refluxed with stirring for 4 hours. The cooled mixture was then treated with water and rendered just acid with a little dilute acetic acid. The ether-soluble material was isolated and the ethereal solution washed with water and dried ($MgSO_4$). The residue, after removal of solvent, was hydrolysed by 3 hours' refluxing with potassium hydroxide (7·5 g.) in aqueous ethanol (40 c.c.). The alkali-soluble material, isolated after dilution and removal of triphenylmethane in ether–benzene, gave an oil which was esterified by 3 hours' refluxing with methanol (80 c.c.) and a little concentrated sulphuric acid. Isolation gave unchanged methyl α-(3-keto-4-methyl*cyclo*hexyl)propionate (4·1 g.), b. p. 73—83°/0·1 mm., n_D^{20} 1·4654, and a fraction (2·5 g.), b. p. 125—135°/0·1 mm., n_D^{20} 1·5175, which was redistilled and gave *methyl* α-(1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-7-*keto*-8 : 10-*dimethyl*-2-*naphthyl*)-*propionate* as a pale yellow oil, b. p. 125—127°/0·1 mm., n_D^{20} 1·5188, $[\alpha]_D$ +21·2° (*c*, 3·9 in chloroform), $\lambda_{max.}$ 245 mμ (log ε 4·05) (Found: C, 72·6; H, 9·2. $C_{16}H_{24}O_3$ requires C, 72·6; H, 9·1%). The 2 : 4-*dinitrophenylhydrazone* formed scarlet prisms, m. p. 166°, from alcohol–ethyl acetate (Found: C, 59·5; H, 6·5. $C_{22}H_{28}O_6N_4$ requires C, 59·4; H, 6·3%).

Dehydrogenation. The foregoing ester (0·9 g.) was hydrogenated (2 mols. absorbed) in acetic acid (20 c.c.) with Adams's platinum oxide, and the product hydrolysed by aqueous-alcoholic potassium hydroxide. The acid, a yellow gum, was treated with selenium (4 g.) at 320—340° for 18 hours. The neutral product recovered from this treatment was distilled from sodium and converted directly into the picrate which formed golden-yellow needles from alcohol and after one recrystallisation from alcohol had m. p. 95°, undepressed on admixture with 7-ethyl-1-methylnaphthalene picrate.

Bromination and Dehydrobromination of Methyl α-(1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-7-*keto*-8 : 10-*dimethyl*-2-*naphthyl*)*propionate*.—The ester (6·5 g.) in carbon tetrachloride (85 c.c.) was heated under reflux for 4 hours with *N*-bromosuccinimide (4·5 g.) and a little benzoyl peroxide. After cooling in ice, succinimide (2·3 g.) was filtered off and the filtrate evaporated *in vacuo*, to give a brown oil which evolved a little hydrogen bromide.

This material was heated under reflux for 2½ hours with dry technical collidine (45 c.c.), and the base hydrobromide (3·9 g.) filtered off after cooling and dilution with ether. The ethereal solution was freed from excess of collidine by washing it with aqueous hydrochloric acid and finally with water. The dried ethereal solution gave on distillation a viscous yellow oil (3·7 g.), b. p. 140—150°/0·4 mm., n_D^{20} 1·5288. This was chromatographed in light petroleum (50 c.c.; b. p. 60—80°) on alumina (100 g.), and the following main fractions were collected, fractions 3 and 4 forming the bulk of the material recovered.

Eluant	n_D^{20}	$\lambda_{max.}$ (mμ) & log ε	Double bonds	Found, % C	Found, % H
(1) Light petroleum–benzene (19 : 1)	1·5220	247 (4·13)	0·9	72·4	9·2
(2) ,, ,, (9 : 1)	1·5224	247 (4·08) 294 (3·51)	—	72·0	9·2
(3) ,, ,, (1 : 1)	1·5235	247 (4·04) 294 (3·96)	1·54	72·4	9·1
(4) Benzene–ether (1 : 1)	1·5338	242 (3·85)	1·98	72·0	8·4

Fraction 4 afforded *methyl* α-(1 : 2 : 3 : 4 : 7 : 10-*hexahydro*-7-*keto*-8 : 10-*dimethyl*-2-*naphthyl*)-*propionate semicarbazone*, m. p. 75°, as a somewhat yellow powder from aqueous methanol, $\lambda_{max.}$ 272 mμ (log ε 4·17) (Found : C, 63·9; H, 7·8. $C_{17}H_{25}O_3N_3$ requires C, 63·95; H, 7·9%).

A small amount of fraction 4 with fuming hydrochloric acid was kept at 35° in a sealed tube for 24 hours. The recovered material, purified by chromatography on alumina followed by distillation in the molecular still gave a resinous solid showing absorption at 212 mμ and 290 mμ (log ε 3·97 and 3·32 respectively).

Pent-1-*yn*-3-*one*.—Pent-1-yn-3-ol (Adams and McGrew, *J. Amer. Chem. Soc.*, 1937, **59**, 1497) was oxidised by chromic acid in acetone (Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39) to *pent*-1-*yn*-3-*one* (45%), b. p. 106°, n_D^{20} 1·4813 (Found : C, 73·1; H, 7·7. C_5H_6O required C, 73·0; H, 7·3%). The 2 : 4-*dinitrophenylhydrazone* formed golden-yellow plates, m. p. 151°, from alcohol–ethyl acetate (Found : C, 50·5; H, 3·9. $C_{11}H_{10}O_4N_4$ requires C, 50·4; H, 3·8%).

Condensation of Methyl α-(3-*Keto*-4-*methyl*cyclo*hexyl*)*propionate with Pent*-1-*yn*-3-*one*.—The ester (6·5 g.) in dry ether (50 c.c.), cooled in ice, was treated with sodiotriphenylmethane (from triphenylmethyl chloride, 11 g., in ether, 250 c.c.) under nitrogen. Pent-1-yn-3-one (2·7 g.) in ether (50 c.c.) was then added with stirring and the mixture kept under nitrogen at 0° for 4 hours and at room temperature overnight. Water was then added and dilute hydrochloric acid to neutrality. The recovered ether-soluble material was hydrolysed by 2 hours' refluxing with potassium hydroxide (2·5 g.) in water (25 c.c.) and alcohol (25 c.c.). From the alkali-soluble material, α-(3-keto-4-methyl*cyclo*hexyl)propionic acid (3·1 g.) was recovered by distillation, and the residue purified by means of sodium hydrogen carbonate and re-esterified by diazomethane. Distillation of the ester gave *methyl* α-(1 : 2 : 3 : 4 : 7 : 10-*hexahydro*-7-*keto*-8 : 10-*dimethyl*-2-*naphthyl*)*propionate*, in small amount, as a viscous yellow oil, b. p. 125°/0·05 mm. (Found : C, 73·1; H, 8·9. $C_{16}H_{22}O_3$ requires C, 73·2; H, 8·4%).

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736. *Formation of Tyrosine Melanin. Part IV.**

By G. R. CLEMO and F. K. DUXBURY.

For a study of the effect of alkyl substituents in the phenylalanine system on melanin formation we have prepared 1-*p*-hydroxybenzylethylamine and several hydroxyphenylalanines.

CONTINUING our work on the assumption that melanin results from the polymerised coupling at certain positions of the 5 : 6-dihydroxyindole system (Clemo and Duxbury, *J.*, 1950, 1795), we have synthesised new alkyl-substituted hydroxyphenylalanines and (by a modification of Woodruff and Conger's method, *J. Amer. Chem. Soc.*, 1938, **60**, 465) 1-*p*-hydroxybenzylethylamine hydrochloride.

2-Methyltyrosine was synthesised from the 2-*p*-methoxyphenylpropaldehyde sodium bisulphite compound. The latter, prepared from anethole essentially by Bougault's method (*Ann. Chim. Phys.*, 1902, **25**, 483), was converted into 5-(1-*p*-methoxyphenylethyl)-hydantoin which was hydrolysed by concentrated hydrochloric acid to 2-methyltyrosine.

5-Allyl-4-hydroxy-3-methoxybenzaldhyde (Claisen and Eisleb, *Annalen*, 1913, **401**, 79) was converted into the azlactone of α-benzamido-β-(4-acetoxy-5-allyl-3-methoxyphenyl)-acrylic acid, hydrolysed to α-benzamido-β-(4-acetoxy-5-allyl-3-methoxyphenyl)acrylic acid and then reduced to α-benzamido-β-(4-acetoxy-3-methoxy-5-*n*-propylphenyl)propionic acid, which on treatment with hydriodic acid and phosphorus yielded 3 : 4-dihydroxy-5-*n*-propylphenylalanine. 2 : 3-Dihydroxy-5-*n*-propylphenylalanine was synthesised similarly from 2-hydroxy-3-methoxy-5-*n*-propylbenzaldehyde, the hydrogenation stage being omitted.

2-Allyl-6-methoxy-*p*-cresol (OH = 1), on treatment with potassium hydroxide, yielded the propenylphenol. The latter on ozonisation and hydrolysis yielded 2-hydroxy-3-methoxy-5-methylbenzaldehyde. This formed the azlactone of α-benzamido-β-(2-acetoxy-3-methoxy-5-methylphenyl)acrylic acid, which was hydrolysed and reduced to 2 : 3-dihydroxy-5-methylphenylalanine.

* Part III, *J.*, 1952, 3464.

Attempts to prepare 2 : 3-dihydroxy-5-methylphenylalanine from 3-ethoxy-2-hydroxy-5-methylphenylacetaldehyde and 2 : 3-dimethoxy-5-methylphenylacetaldehyde failed.

4 : 5-Dimethoxy-2-*n*-propylbenzyl chloride condensed with acetamidomalonic ester, and the product was hydrolysed and decarboxylated with alcoholic potassium hydroxide to form α-acetamido-β-(4 : 5-dimethoxy-2-*n*-propylphenyl)propionic acid which was converted into 4 : 5-dihydroxy-2-*n*-propylphenylalanine with hydriodic acid.

An attempt to synthesise 3 : 4-dihydroxy-2-methylphenylalanine from α-benzamido-β-(4-hydroxy-3-methoxy-2-methylphenyl)acrylic acid was unsuccessful. A method similar to that of Cromartie and Harley-Mason (*J.*, 1952, 1053) was, however, successful.

The action of tyrosinase on the above compounds will be reported later.

Experimental

DL-3 : 4-*Dihydroxy*-5-n-*propylphenylalanine*.—5-Allyl-4-hydroxy-3-methoxybenzaldehyde (3 g.), hippuric acid (3 g.), anhydrous sodium acetate (1·5 g.), and acetic anhydride (10 ml.) were heated on a water-bath for 45 minutes, then cooled, and, after the addition of water, warmed again for 15 minutes. The yellow product was filtered off, washed with hot water, and recrystallised from acetic acid.

The *azlactone* of α-benzamido-β-(4-acetoxy-5-allyl-3-methoxyphenyl)acrylic acid was obtained as a yellow solid (4·5 g.), m. p. 153° (Found : C, 70·0; H, 5·1. $C_{23}H_{19}O_5N$ requires C, 70·0; H, 5·0%). The azlactone (4 g.), sodium hydroxide (1·8 g.), and 50% aqueous ethanol (60 ml.), were warmed on a water-bath for 15 minutes, water (120 ml.) was added to the deep red solution, and 20% hydrochloric acid added dropwise with stirring until the acid was precipitated. The *α-benzamido-β-(4-acetoxy-5-allyl-3-methoxyphenyl)acrylic acid* was recrystallised from 50% ethanol (charcoal) (yield, 2·0 g.), and had m. p. 207° (Found : C, 66·7; H, 5·1. $C_{22}H_{21}O_6N$ requires C, 66·8; H, 5·3%).

The acrylic acid (10 g.), acetic acid (100 ml.), and 5% palladium–charcoal (0·75 g.) were shaken under hydrogen (100 lb./sq. in.) for 12 hours. The acetic acid was distilled off, and the residue recrystallised from acetic acid, giving *α-benzamido-β-(4-acetoxy-3-methoxy-5-n-propylphenyl)propionic acid* (9·0 g.), m. p. 200° (Found: C, 65·8; H, 6·2. $C_{22}H_{25}O_6N$ requires C, 66·2; H, 6·3%).

This acid (5 g.), hydriodic acid (27 ml.; *d* 1·7), acetic anhydride (27 ml.), and red phosphorus (2·3 g.) were refluxed under a slow stream of hydrogen for 2 hours. Water was added, the phosphorus filtered off, the red filtrate extracted three times with ether, and the aqueous layer evaporated in a stream of hydrogen under reduced pressure. The semisolid hydriodide was dissolved in water (100 ml.), and passed down a column of De-acidite E (2 × 35 cm.), at 5 ml./min. The column was washed with water until the effluent was colourless. The resulting purple solution was decolorised with sulphur dioxide and evaporated to dryness over concentrated sulphuric acid *in vacuo*. The white residue was twice recrystallised from water containing a little sulphur dioxide (charcoal), yielding 3 : 4-*dihydroxy*-5-n-*propylphenylalanine* (1·0 g.), m. p. 278—280° (Found : C, 55·8; H, 7·5. $C_{12}H_{17}O_4N,H_2O$ requires C, 56·0; H, 7·4. Found, after drying in a vacuum over concentrated sulphuric acid : C, 60·8; H, 7·2. $C_{12}H_{17}O_4N$ requires C, 60·3; H, 7·1%). The amino-acid was soluble in water, gave a positive ninhydrin test and a blue-black colour with ferric chloride, and reduced silver nitrate solution.

DL-2 : 3-*Dihydroxy*-5-n-*propylphenylalanine*.—To a stirred mixture of dihydroeugenol (37 g.), ethanol (90 ml.), sodium hydroxide (75 g.), and water (157 ml.) at 80—90°, chloroform (39 ml.) was added during 1 hour and the resulting mixture heated for a further 2 hours, steam-distilled, and then saturated with sulphur dioxide. The mixture was shaken for 1 hour with sodium hydrogen sulphite (25 g.). The resulting semisolid mass was shaken with ether, centrifuged to separate the layers, and filtered. The solid bisulphite complex was washed with ether and decomposed with 10% sulphuric acid (30 ml.) on a water-bath. The brown oil so formed was extracted with ether and dried ($CaCl_2$), the solvent removed, and the *2-hydroxy-3-methoxy*-5-n-*propylbenzaldehyde* distilled as a pale yellow oil, b. p. 115—120°/1 mm. (Found : C, 67·9; H, 7·1. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%).

The aldehyde (6 g.), hippuric acid (6 g.), anhydrous sodium acetate (3 g.), and acetic anhydride (15 ml.) gave, as in the previous case, the *azlactone* of α-benzamido-β-(2-acetoxy-3-methoxy-5-*n*-propylphenyl)acrylic acid as a yellow solid (9 g.), m. p. 150° (Found : C, 69·6; H, 5·4. $C_{22}H_{21}O_5N$ requires C, 69·6; H, 5·5%).

The azlactone (4 g.), 50% ethanol (60 ml.), and sodium hydroxide (1·8 g.) gave, as in the

previous case, *α-benzamido-β-(2-hydroxy-3-methoxy-5-n-propylphenyl)acrylic acid*, (3·4 g.), m. p. 202—203° (from 50% ethanol) (Found: C, 67·6; H, 6·0. $C_{20}H_{21}O_5N$ requires C, 67·6; H, 5·9%).

The acrylic acid (1 g.), hydriodic acid (7 ml.), acetic anhydride (7 ml.), and red phosphorus (0·7 g.) were refluxed under hydrogen for 1½ hours. The phosphorus was filtered off, the filtrate extracted three times with ether, and the aqueous layer evaporated under hydrogen. The dark residue was treated with charcoal in water (20 ml.) containing a little sulphur dioxide, and the resulting pale yellow solution was treated dropwise with aqueous ammonia (*d* 0·88) till the solid acid separated. The 2 : 3-*dihydroxy*-5-n-*propylphenylalanine* was filtered off, redissolved in a minimum amount of dilute hydrochloric acid, and treated with charcoal, and aqueous ammonia once more added until the acid (0·3 g.), m. p. 260°, separated (Found: C, 60·3; H, 7·1. $C_{12}H_{17}O_4N$ requires C, 60·25; H, 7·1%). The amino-acid is sparingly soluble in water, gives a positive ninhydrin test and a blue-black colour with ferric chloride, and reduces silver nitrate solution.

DL-2 : 3-*Dihydroxy*-5-*methylphenylalanine*.—Vanillin (60 g.), water (113 ml.), concentrated hydrochloric acid (263 ml.), toluene (150 ml.), ethanol (40 ml.), and zinc amalgam (180 g.) were refluxed for 48 hours. Concentrated hydrochloric acid (38 ml.) was added every 6 hours. The toluene layer was separated and the aqueous layer extracted twice with toluene. The toluene solution was dried ($MgSO_4$) and the solvent removed. 2-Methoxy-*p*-cresol (OH = 1) distilled as a colourless liquid (30 g.), b. p. 102—105°/15 mm. (Found: C, 69·6; H, 7·55. Calc. for $C_8H_{10}O_2$: C, 69·5; H, 7·25%).

2-Allyl-6-methoxy-*p*-cresol (OH = 1) (30 g.) (Kawai, *Ber.*, 1939, **72**, 376), ethanol (400 ml.), and potassium hydroxide (120 g.) were refluxed for 60 hours. The ethanol was distilled off, and sufficient water added to dissolve the residue. The resulting solution was acidified with hydrochloric acid (50%) and steam-distilled. 2-*Methoxy*-6-*propenyl*-p-*cresol* (OH = 1) recrystallised from ethanol–water as needles (16 g.), m. p. 60—62° (Found: C, 74·6; H, 8·0. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·8%). A solution of this (5 g.) in ethyl acetate (30 ml.) was cooled in ice–salt and ozonised (5%) until excess of ozone could be detected leaving the solution (potassium iodide–starch). The solvent was removed under reduced pressure at $< 50°$ (care!). The resulting pale yellow, syrupy ozonide was treated with water (25 ml.) and steam-distilled, yielding 2-hydroxy-3-methoxy-5-methylbenzaldehyde as pale yellow needles (2·5 g.), m.p. 74—75° (Found: C, 64·8; H, 6·4. Calc. for $C_9H_{10}O_3$: C, 65·1; H, 6·0%).

The aldehyde (5 g.), hippuric acid (5 g.), anhydrous sodium acetate (2·5 g.), and acetic anhydride (10 ml.) were heated on a water-bath for 1 hour. Water (30 ml.) was added and the yellow product warmed, filtered off, washed with hot water, and recrystallised from acetic acid. The *azlactone* of α-benzamido-β-(2-acetoxy-3-methoxy-5-methylphenyl)acrylic acid was obtained as yellow needles (7·5 g.), m. p. 198—200° (Found: C, 68·7; H, 4·9. $C_{20}H_{17}O_5N$ requires C, 68·4; H, 4·8%).

The azlactone (5 g.), hydriodic acid (20 ml.), acetic anhydride (20 ml.), and red phosphorus (2·1 g.) were refluxed under hydrogen for 4 hours. Treatment as in the first case above yielded 2 : 3-*dihydroxy*-5-*methylphenylalanine* (1·0 g.), m. p. 278—280° (Found: C, 57·2; H, 6·2. $C_{10}H_{13}O_4N$ requires C, 56·9; H, 6·1%). The amino-acid possessed properties similar to those described previously.

DL-4 : 5-*Dihydroxy*-2-n-*propylphenylalanine*.—4 : 5-Dimethoxy-2-*n*-propylbenzyl chloride (5·0 g.) (Mr. R. W. TEMPLE, unpublished work), acetamidomalonic ester (4·8 g.), ethanol (35 ml.), and sodium (0·5 g.) were refluxed for 6 hours. Sodium chloride was filtered off and the solvent removed under reduced pressure. The residual pale yellow oil was treated with 20% ethanolic sodium hydroxide (25 ml.), heated under reflux for 1 hour, cooled, and acidified with 3N-hydrochloric acid. The precipitate was filtered off, boiled an hour with N-hydrochloric acid, cooled, and filtered off. *α-Acetamido-β-(4 : 5-dimethoxy*-2-n-*propylphenyl)propionic acid*, recrystallised from water, had m. p. 165—166° (3·0 g.) (Found: C, 62·3; H, 7·5. $C_{16}H_{23}O_5N$ requires C, 62·1; H, 7·4%). The acid (3·5 g.), hydriodic acid (20 ml.), acetic anhydride (20 ml.), and red phosphorus (2 g.) were refluxed under hydrogen for 3 hours and then treated with water (25 ml.), evaporated to dryness in a stream of hydrogen under reduced pressure, and worked up as above, yielding 4 : 5-*dihydroxy*-2-n-*propylphenylalanine* (2·0 g.), m. p. 260—261° (Found: C, 58·3; H, 7·4. $C_{12}H_{17}O_4N,\frac{1}{2}H_2O$ requires C, 58·1; H, 7·3%). The amino-acid gives the usual reactions with ninhydrin, ferric chloride, and silver nitrate.

3-*Ethoxy*-2-*hydroxy*-5-*methylphenylacetaldehyde*.—*O*-Ethylvanillin (20 g.), water (37 ml.), concentrated hydrochloric acid (87 ml.), toluene (50 ml.), ethanol (40 ml.), and zinc amalgam (60 g.), by treatment as in the analogous case above, afforded 2-*ethoxy*-p-*cresol* (OH = 1) as

a colourless liquid (12 g.), b. p. 105—108°/15 mm., m. p. 34° (Found: C, 70·9; H, 8·0. $C_9H_{12}O_2$ requires C, 71·05; H, 7·9%).

This phenol (30 g.), allyl bromide (27 g.), acetone (55 ml.), and anhydrous potassium carbonate (37 g.) were refluxed for 12 hours. Sufficient water was added to dissolve the carbonate, and the mixture was extracted three times with ether. The ethereal layer was washed with N-sodium hydroxide and then water, dried ($CaCl_2$), and evaporated. The pale yellow residual oil was heated at 210—230° until boiling ceased. The resulting dark liquid was distilled, yielding *2-allyl-6-ethoxy-p-cresol* (OH = 1), a colourless liquid, rapidly becoming green in air (26 g.), b. p. 132—134°/15 mm. (Found: C, 75·3; H, 8·7. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%).

The above (9·3 g.), methanol (50 ml.), anhydrous potassium carbonate (3·3 g.), and benzyl chloride (6·9 g.) were refluxed for 24 hours. Methanol and excess of benzyl chloride were removed, sufficient water was added to dissolve the carbonate, and the aqueous solution extracted with ether. The ethereal extract was washed with aqueous sodium hydroxide and then water, dried ($CaCl_2$), and evaporated. *1-Allyl-2-benzyloxy-3-ethoxy-5-methylbenzene* was obtained as a colourless liquid (9·0 g.), b. p. 195—197°/15 mm. (Found: C, 80·8; H, 8·0. $C_{19}H_{22}O_2$ requires C, 80·85; H, 7·8%). *Ethyl 2-allyl-6-ethoxy-4-methylbenzoate* was obtained as a colourless liquid, b. p. 153—155°/15 mm. (Found: C, 68·5; H, 7·6. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%). *1-Allyl-3-ethoxy-2-methoxy-5-methylbenzene* was obtained as a colourless liquid, b. p. 128—130°/15 mm. (Found: C, 75·7; H, 9·2. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·7%).

2-Allyl-3-ethoxy-*p*-cresol (6 g.), in ethyl acetate (50 ml.), cooled in acetone–solid carbon dioxide, was ozonised (5%) until excess of ozone could be detected. After 20 minutes palladium–charcoal (0·5 g.) was added and the mixture shaken with hydrogen until no further uptake could be detected. The catalyst was filtered off, the filtrate shaken with aqueous sodium hydrogen carbonate and then water, and dried ($CaCl_2$). The solvent was removed and the residue cooled. The semisolid mass was filtered off and the *2-hydroxy-3-ethoxy-5-methylphenylacetaldehyde* recrystallised from ether; it (2·5 g.) had m. p. 95—96° (Found: C, 68·2; H, 7·7. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%).

2-Ethoxy-6-propenyl-p-cresol (OH = 1).—The allylphenol (30 g.), ethanol (400 ml.), and potassium hydroxide (120 g.) were refluxed for 48 hours. The ethanol was distilled off, sufficient water to dissolve the residue added, and the solution acidified with 50% hydrochloric acid and steam-distilled. *2-Ethoxy-6-propenyl-p-cresol* crystallised from ethanol–water as needles (15 g.), m. p. 73—74° (Found: C, 75·0; H, 8·6. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%).

2 : 3-Dimethoxy-5-methylphenylacetaldehyde.—2-Allyl-6-methoxy-*p*-cresol (Kawai, *loc. cit.*) (29 g.), methanol (64 ml.), and methyl sulphate (27 ml.) were stirred in ice–salt. Sodium hydroxide (23 g.) in water (58 ml.) was slowly added. After 30 minutes the mixture was extracted with ether, washed with 10% aqueous sodium hydroxide and then water, dried (Na_2SO_4), and evaporated. *1-Allyl-2 : 3-dimethoxy-5-methylbenzene* was distilled, as a colourless liquid (25 g.), b. p. 120—124°/14 mm. (Found: C, 74·8; H, 8·5. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%).

A solution of the above (5 g.) in ethyl acetate (30 ml.), was ozonised (5%) and worked up as in the previous case. Final distillation (care !) gave *2 : 3-dimethoxy-5-methylphenylacetaldehyde* as a pale yellow liquid (2·0 g.), b. p. 115—120°/1 mm. (Found: C, 68·55; H, 7·4. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%). The *p-nitrophenylhydrazone* had m. p. 170° (Found: C, 62·1; H, 6·2. $C_{17}H_{19}O_4N_3$ requires C, 62·0; H, 5·8%).

DL-*2-Methyltyrosine.*—Finely powdered iodine (40 g.) was added in small portions, during ½ hour, to a stirred mixture of anethole (25 g.), ether (100 ml.) saturated with water, and freshly prepared yellow mercuric oxide (40 g.). After each addition the orange colour was permitted to return before more iodine was added. The mixture was warmed for 10 minutes, left overnight, and filtered. The filtrate was shaken with sodium hydrogen sulphite solution (*d* 1·34), and the resulting semisolid mass was kept for 2 hours and filtered. The bisulphite compound of *2-p-methoxyphenylpropaldehyde* was recrystallised from water (yield, 14 g.). The compound (2·0 g.), ammonium carbonate (2·4 g.), potassium cyanide (0·52 g.), and aqueous ethanol (12 ml.) were heated in a sealed tube for 4 hours at 100°. The contents were then diluted with water (8 ml.), and the resulting mixture heated for 20 minutes at 105—110° to decompose the excess of ammonium carbonate. The solid was then filtered off, after cooling, and washed with a little water. The *5-(1-p-methoxyphenylethyl)hydantoin*, recrystallised from ethanol (yield, 0·9 g.), had m. p. 203—205° (Found: C, 61·2; H, 6·2. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0%).

The hydantoin (0·5 g.) and concentrated hydrochloric acid (5 ml.) were heated in a sealed tube for 4½ hours at 155—160°, then cooled, water (12 ml.) was added, and the mixture filtered. The pH of the boiling solution was adjusted to 6 with ammonium hydroxide (*d* 0·88), treated with

charcoal, and filtered. The resulting solution was reduced to 5—10 ml. *in vacuo* and the acid filtered off. DL-2-*Methyltyrosine*, recrystallised from water (charcoal), had m. p. 263—265° (0·25 g.) (Found: C, 61·4; H, 6·9. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·7%).

DL-1-p-*Hydroxybenzylethylamine Hydrochloride*.—Sodium amalgam (4%; 200 g.) was added during ½ hour to a stirred mixture of *p*-methoxy-α-methylcinnamic acid (12 g.), and 10% sodium hydroxide solution (50 ml.). The solution was then warmed on a water-bath until reaction had ceased, filtered, and acidified with 3N-hydrochloric acid. The yellow oil was extracted with chloroform, the extract dried ($MgSO_4$), and the solvent removed. Thionyl chloride (10 ml.) was added to the resulting yellow oil, and the mixture refluxed for 3 hours. Excess of thionyl chloride was removed *in vacuo*, the residue poured into aqueous ammonia (*d* 0·88), and after 1 hour the solid was filtered off. α-p-*Methoxybenzylpropionamide*, recrystallised from aqueous alcohol, had m. p. 126° (9 g.) (Found: C, 67·8; H, 7·7. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8%).

The amide (6·0 g.) was added to an ice-cold solution of bromine (6·0 g.) in 10% potassium hydroxide solution (90 ml.), the mixture shaken for about 20 minutes and then filtered, and the filtrate heated at 70—80° for 90 minutes. Sodium hydroxide (5·0 g.) was then added, the mixture heated at 80° for 2 hours, cooled, and extracted with ether. The extract was dried ($MgSO_4$), filtered, and treated with hydrogen chloride. 1-*p*-Methoxybenzylethylamine hydrochloride was filtered off and recrystallised from ether–ethanol (5·0 g.), m. p. 204° (Found: C, 59·6; H, 7·9. Calc. for $C_{10}H_{16}ONCl$: C, 59·8; H, 8·2%).

Bougault's method (*loc. cit.*) gave a material which, on treatment with ether, solidified and from ethanol–ether afforded 1-*p*-hydroxybenzylethylamine hydrochloride (0·7 g.), m. p. 169—170° (Found: C, 57·6; H, 7·7. Calc. for $C_9H_{14}ONCl$: C, 57·6; H, 7·5%).

α-*Benzamido*-β-(4-*hydroxy*-3-*methoxy*-2-*methylphenyl*)*acrylic Acid*.—4-Hydroxy-3-methoxy-2-methylbenzaldehyde (5 g.), anhydrous sodium acetate (3 g.), hippuric acid (6 g.), and acetic anhydride (20 ml.) yielded, as in previous cases, the *azlactone* of α-benzamido-β-(4-acetoxy-3-methoxy-2-methylphenyl)acrylic acid as yellow needles (5 g.) (dried at 120—130°), m. p. 153—155° (Found: C, 68·3; H, 4·7. $C_{20}H_{17}O_5N$ requires C, 68·3; H, 4·8%).

The azlactone (5 g.), sodium hydroxide (2·0 g.), and 50% aqueous ethanol (60 ml.) were warmed on a water-bath for 15 minutes, affording, as above, α-*benzamido*-β-(4-*hydroxy*-3-*methoxy*-2-*methylphenyl*)*acrylic acid* (1 g.), m. p. 270—271° (from acetic acid) (Found: C, 66·0; H, 4·9. $C_{18}H_{17}O_5N$ requires C, 66·1; H, 5·2%).

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737. *The Use of the Spekker Photoelectric Absorptiometer for the Determination of* pH.

By T. B. SMITH, C. A. WHITE, P. WOODWARD, and P. A. H. WYATT.

The use of several buffer solutions to determine the pK of an indicator not only provides an essential datum but also enables the suitability of the indicator for the proposed method to be tested. Precautions are considered whereby the sum of the errors of measurement and of the assessment of activity effects may be kept within desired limits. If the recommended procedure is adopted, the pK may be determined to within 0·02 unit, and in favourable cases to better than 0·01. pK values are determined for the nitrophenols, and the behaviour of methyl-red is considered in some detail.

LOTHIAN (*Trans. Faraday Soc.*, 1937, **33**, 1239) proposed the use of the Spekker photoelectric absorptiometer for determination of pH with a white light source and special filters, and gave calibration curves for several indicators. Such curves would give accurate results only for solutions of about the same ionic strength as that of the buffer solutions used in the calibration. Moreover, the method requires the accurate reproduction of concentrations of stock indicator solutions—an exacting requirement—and does not use the simple relation between drum-readings and concentrations which should make applicable an indicator equation of the Ostwald type, *viz.*, $HIn \rightleftharpoons H^+ + In^-$ (HIn = indicator). By contrast, the method described below utilises the capacity of the Spekker

instrument to measure optical density, and its validity has been demonstrated by the accurate determination of pK_{In} values for some common indicators.

From the equation defining the dissociation constant (K_{In}) of a typical simple indicator of the pseudo-acid type it follows that

$$pK_{In} = p\{H^+\} + \log_{10}[HIn]/[In^-] + \log_{10} f_{HIn}/f_{In^-} \quad . \quad . \quad . \quad . \quad (1)$$

(see T. B. Smith, "Analytical Processes," Edward Arnold & Co., London, 1940, pp. 229—231). An analogous formula can be applied to a pseudo-base. In equation (1) the relation between pK_{In} and $p\{H^+\}$ can be derived if the other two terms can be determined. Measurement of the ratio $[HIn]/[In^-]$ by means of absorptiometer is equivalent in principle to determination of the concentration of one species only, since a wave-length would be chosen to exclude the other. Hence, ideally, water would be suitable for establishing one of the scale-readings required; but since some departure from ideal conditions is often inevitable, it is safer to use the extreme colour of the indicator for this purpose. Any solution of pH not less than 3 units from the pK is suitable. The concentration of other species will then be not greater than 0·1%. Cases where such a simple arrangement is not practicable are discussed later.

If α and β are the Spekker drum-readings corresponding with the fully non-ionised and with the fully ionised condition respectively, and if R is the reading for an intermediate state, then

$$[HIn]/[In^-] = (R - \beta)/(\alpha - R) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

This ratio should be evaluated accurately, especially for determination of pK which enters into any subsequent calculation of pH.

The term $\log (f_{HIn}/f_{In^-})$ of equation (1) involves assessment of activity effects. Unless the solutions are unduly concentrated, it should be possible to calculate these effects from one of the well-known approximate equations. Of these, by far the most convenient is Davies's form (*J.*, 1938, 2093) since, unlike such earlier equations as those of Debye and Hückel, Brønsted, and Guggenheim, it contains no constants which have to be specially evaluated for each application. This simplification may, of course, lead to some loss of accuracy, but that the equation is entirely adequate for present purposes is shown in the Experimental section in connection with the preparation of buffers.

The activity coefficient, f_i, of an ion of valency z_i at 25° is then represented by

$$\log f_i = -0{\cdot}5\, z_i^2 \phi(I) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where I is the ionic strength and

$$\phi(I) = \sqrt{I}/(1 + \sqrt{I}) - 0{\cdot}2(I)$$

Equation (1) then becomes

$$pK_{In} = p\{H^+\} + \log [HIn]/[In^-] + 0{\cdot}5\phi(I) \quad . \quad . \quad . \quad . \quad . \quad (4)$$

since f_{HIn} may be taken as unity.

Experimental

Instrument.—For approximate work the Spekker Photoelectric Absorptiometer model H 560 can be used as supplied by the makers; for the highest accuracy, however, a few modifications to the instrument were made, and certain precautions observed.

(*a*) *Voltage stabilisation.* A BISRA study group has concluded that, for many purposes, most instruments are sufficiently self-compensating to eliminate effects of the usual voltage fluctuations. This property depends on the critical matching of the photocells, and, in the instrument used in these investigations, changes of drum-reading of about 0·02 unit were observed for a 5-v change in the supply when a Wratten 74 (green) filter was used. Consequently the voltage used in all the experiments described here was controlled at 195 ± 0·5 volts, by a carbon-pile regulator.

(*b*) *Temperature effects.* (i) The perceptible absorption of the usual heat filters in the visible spectrum alters appreciably for the temperature increases which inevitably occur when light is being transmitted. The only simple cure is to permit passage of light for very short intervals of time. The gelatin light-filters may also be affected if placed adjacent to the heat-filters, but an improvised position on the opposite side of the glass cell (except when 4-cm. cells render this impossible) practically eliminates the effect. (The Spekker model H 760 has incorporated a

filter holder in this position.) (ii) Both indicator and buffer characteristics may vary with temperature, and consequently temperature control is essential for accurate work. This was achieved by storing the solutions in a thermostat at 28° and allowing them to cool in the cell on the instrument at a known rate, to 25° ± 0·1°. The glass cells were also fitted with cover slips to eliminate evaporation, to reduce the rate of cooling, and to minimise meniscus reflections by facilitating complete filling of the cells. (iii) The general heating of the apparatus from the lamp causes an additional (and avoidable) change in the transmission of the filters. It is also liable to produce a shift of the light image relative to the photocell surface; this image is larger than the photocell surface and is of non-uniform intensity. The use of a water-cooled lamp-house minimises these effects and has other advantages; its adoption follows the practice of the Bragg Laboratory, N.O.I.D., Sheffield.

(*c*) *The light beam.* Since the mercury-arc lamp does not provide a point source, the resulting beam cannot be both parallel and of uniform intensity; for large apertures considerable divergence occurs. This causes the beam to strike the bottom of the glass cells with consequent variable reflection errors. (If the cell is raised to avoid meniscus reflections at the liquid surface, there is even a danger of the light passing through the glass base of the cell.) In all experiments recorded here, apertures larger than correspond to a drum-reading of 0·2 were therefore avoided. Photocell fatigue effects were also thereby reduced.

(*d*) *Extraneous light.* This should be excluded as far as possible. All the cells were covered with black " Perspex " hoods during use.

(*e*) *The calibrated aperture.* A check should be made on all sections of the scale within the working limits, with a neutral filter of low optical density (*e.g.*, H 503). The Spekker used was satisfactory in this respect.

Procedure for the Accurate Determination of pK_{In}, *the Approximate Value being known.*—In all determinations a mercury-arc lamp, with appropriate heat- and light-filters, was used, to give an effectively monochromatic source. A series of buffer solutions covering the range of about 1 unit of pH on either side of the change-point of the indicator, and a stock solution of the indicator itself (preferably in water), were first prepared. Each of the buffer solutions was then mixed with 5 ml. of indicator solution and diluted so as to give a total volume of 100 ml. Standards for the " acid " and " alkaline " forms of the indicator were produced from any solution of pH at least 3 units from the change-point of the indicator in question. Mineral acid and alkali of approximately N/100 concentration were convenient for the nitrophenols. Difficulties may arise if the indicator has more than one change-point, in which case extrapolation methods can be employed (see results for methyl-red). Indicator concentrations were chosen so that the 4-cm. glass cells could be used to give readings between 0·2 and 0·9 on the drum. The fully coloured form was used as the standard, and was rechecked at frequent intervals during each determination, but no wandering of the drum-reading was observed when the precautions outlined above were taken. Filters were chosen to transmit light of wave-length as near as possible to the absorption maximum of the indicator.

Nitrophenols.—The behaviour of simple indicators of the pseudo-acid type, such as nitrophenols, is adequately represented by equation (4). The more highly coloured (alkaline) form of the indicator is represented by In^-, so that, from equations (2) and (4), we obtain

$$pK_{In} = p\{H^+\} + \log(R - \beta)/(\alpha - R) + 0{\cdot}5\phi(I) \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The several values of pK_{In} shown in Tables 1—3 for *m*-, *p*-, and *o*-nitrophenol have been calculated with the aid of this equation.

Methyl-red (p-*Dimethylaminoazobenzene*-o-*carboxylic Acid*).—This exemplifies relatively complicated cases. Since methyl-red contains both a basic and an acidic group, changes are produced (i) by addition of a proton to the basic nitrogen atom in more acid solutions, forming a singly charged cation, *i.e.*, $HIn + H^+ \rightleftharpoons H_2In^+$ (ion of quaternary salt, known as Red I), and (ii) by reversal of this process in more alkaline solution, and ionisation of the carboxyl group producing a singly charged anion, $HIn \rightleftharpoons H^+ + In^-$ (ion of yellow salt). There is some doubt whether the intermediate form (Red II) is properly represented as an uncharged molecule (HIn), or as a zwitterion ($^+HIn^-$) (see Kolthoff, " Acid-base Indicators," The MacMillan Co., New York, 1937, p. 146). For present purposes the former assumption is made, and the activity coefficient of HIn is taken to be 1 at the concentrations used (see, however, p. 3853). Then

$$K_1 = \{H^+\}[HIn]/[H_2In^+]f_I \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$K_2 = \{H^+\}[In^-]f_I/[HIn] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where f_I represents the activity coefficient of a univalent ion.

At the wave-length used, the absorption of Red I is less than that of Red II and, because of some overlap of the two indicator stages, there is in the region of pH 3—4 a minimum in the drum-readings which does not correspond with the indicator's being wholly in the Red II form. The drum-reading for the latter condition, though inaccessible to direct measurement, can be derived by calculation. Thus, let a, b, c, respectively denote drum-readings which correspond ideally with the indicator's being wholly in the forms H_2In^+, HIn, and In^- respectively; further let R (or R') represent any other reading between a and b (or b and c). Then the ratios $[HIn]/[H_2In^+]$ and $[In^-]/[HIn]$ in equations (6) and (7) become respectively $(a - R)/(R - b)$ [and $(R' - b)/(c - R')$] for all solutions in which one of the three forms is negligible. Hence, from equation (6),

$$R = (a - R)\{H^+\}/f_1(K_1) + b \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

and, from equation (7),

$$R' = [K_2(c - R')/\{H^+\}f_1] + b. \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

It is clear that, by plotting R against the coefficient of $1/K_1$ in equation (8), and R' against the coefficient of K_2 in equation (9), two independent values of b can be derived as the intercepts on the axis of R. The relevant experimental data are quoted in Tables 4 and 5, where values of the coefficients of $1/K_1$ and K_2 are given (column 4). The divergencies from linearity are negligible. Application of the method of least squares to the data gave:

$$pK_1 \text{ range}: b = 0{\cdot}197; \; pK_1 = 2{\cdot}33;$$
$$pK_2 \text{ range}: b = 0{\cdot}203; \; pK_2 = 5{\cdot}01.$$

The agreement between the b values obtained from the two ranges is reasonable but, in view of the small difference in drum-readings involved in the pK_1 measurements, the b values from the pK_2 range are regarded as much more reliable. For the present purpose, it is of interest to investigate the variability of pK as obtained from individual buffers; by using, therefore, $b = 0{\cdot}203$, the pK_2 values recorded in column 5 of Table 5 have been obtained.

For these calculations it has been assumed, as a first approximation, that the constant a was measured sufficiently accurately by use of 0·1N-hydrochloric acid. The approximate pK_1 values so obtained show, however, that in such an acid there would remain about 4% of Red II; accordingly, a more accurate value of a has been calculated by simple proportion and used in deriving the pK_1 values of Table 4.

Materials.—*m*-Nitrophenol was of B.D.H. Indicator quality; the stock solution contained 0·26 g./l. *p*-Nitrophenol was of B.D.H. Indicator quality; the stock solution contained 0·025 g./l. *o*-Nitrophenol was resublimed; the stock solution contained 0·1 g./l. Methyl red of B.D.H. Indicator quality was recrystallised; the stock solution contained 0·02 g./l.

Phosphate buffers. $\{pH^+\}$ values for NaH_2PO_4–Na_2HPO_4 mixtures (of "AnalaR" quality) (of ionic strength shown in Tables 1—3) were derived from the tables of Cohn *et al.* (*J. Amer. Chem. Soc.*, 1927, **49**, 173; 1928, **50**, 696).

Borax buffers. 0·05M-Borax of "AnalaR" quality was used. $p\{H^+\} + 0{\cdot}5\phi(I)$ at 25° = 9·29 (see Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, 1943, p. 321).

Acetate buffers. The $p\{H^+\}$ values for sodium acetate–acetic acid mixtures have been calculated by the Davies formula (equation 3) with pK_a for acetic acid = 4·756 (from the best values quoted by Harned and Owen, *op. cit.*, p. 515). Values calculated in this way were in excellent agreement with the experimental standards quoted by Harned and Owen, *op. cit.*, p. 321).

Results.—See Tables.

TABLE 1. pK_{In} *for* m-*nitrophenol.* Filters: Wratten 2 and Chance OV 1, giving mainly the Hg line 4047 Å.

$p\{H^+\} + 0{\cdot}5\phi(I)$		Drum reading	I	$0{\cdot}5\phi(I)$	pK_{In}
N/100-H_2SO_4		0·801			
N/100-NaOH		0·300			
6·95	PO_4''' buffers	0·784	0·100	0·110	(8·40)
7·55		0·730	0·130	0·120	8·33
7·65		0·720	0·160	0·127	8·36
7·94		0·664	0·151	0·124	8·36
8·34		0·560	0·150	0·124	8·37
9·29	Borax buffer	0·364	0·100	0·110	8·35

TABLE 2. pK_{In} *for* p-*nitrophenol.* Filters as for *m*-nitrophenol.

N/100-H_2SO_4		0·899			
N/100-NaOH		0·300			
6·35	PO_4''' buffers	0·817	0·07	0·098	7·14
6·64		0·665	0·10	0·110	7·14
6·95		0·753	0·10	0·110	7·13
7·23		0·576	0·14	0·122	7·17
7·55		0·471	0·13	0·120	7·15

TABLE 3. pK_{In} *for* o-*nitrophenol.* Filters: Wratten 50 and Chance OB 2, giving mainly the Hg line 4360 Å.

N/100-H_2SO_4		0·766			
N/100-NaOH		0·250			
6·35	PO_4''' buffers	0·692	0·07	0·098	7·13
6·64		0·650	0·10	0·110	7·17
6·95		0·573	0·10	0·110	7·17
7·23		0·491	0·14	0·122	7·18
7·55		0·420	0·13	0·120	7·14

TABLE 4. *Methyl-red:* pK_1 *for the range Red I to Red II.* Filters: Wratten 74 and H 503, giving mainly the Hg line 5461 Å. $a = 0·304$, calc. from an observational mean of 0·301 for N/10-hydrochloric acid; $b = 0·203$.

HCl normality (also = I)	p{H⁺}	R	$10^4(0·301 - R)\{H^+\}/f_I$	pK_1
0·01910	1·78	0·281	3·82	2·25
0·01433	1·90	0·275	3·72	2·24
0·00955	2·06	0·267	3·24	2·26
0·00478	2·35	0·249	2·48	2·24
0·00239	2·64	0·234	1·60	2·27
0·001433	2·86	0·220	$1·16_2$	2·14
0·000955	3·03	0·215	$0·82_1$	2·14

TABLE 5. *Methyl-red:* pK_2 *for the range Red II to yellow.* Acetate buffers. Filters as for pK_1. $c = 0·842$ (mean of 10 readings for N/100-NaOH); $b = 0·203$.

p{H⁺}	R'	I	$10^{-4}(c - R')/\{H^+\}f_I$	pK_2
4·51	0·373	0·0250	1·782	5·02
4·68	0·430	0·0313	2·345	5·01
4·85	0·496	0·0375	2·958	5·00
5·04	0·564	0·0438	3·698	5·01
5·27	0·644	0·0500	4·52	5·01
5·62	0·735	0·0563	5·49	5·01
		Buffers made 0·05M *with respect to* NaCl.		
4·48	0·362	0·0750	1·824	5·06
4·65	0·420	0·0813	2·400	5·04
4·83	0·485	0·0875	3·058	5·04
5·02	0·550	0·0938	3·89	5·05
5·25	0·638	0·1000	4·65	5·03
		Buffers made 0·033M *with respect to* $BaCl_2$.		
4·48	0·364	0·0750	1·817	5·05
4·65	0·430	0·0813	2·348	5·02
4·83	0·490	0·0875	3·010	5·02
5·02	0·559	0·0938	3·768	5·03
5·25	0·636	0·1000	4·71	5·04
5·60	0·731	0·1063	5·70	5·03

TABLE 6. *Summary of mean* pK *values for methyl-red.*

		Theor. method ($f_{HIn} = 1$)	Empirical method ($f_{HIn} = f_I$)
b		0·203	0·186
pK_2	Buffers without additional salt	5·01 ± 0·01	4·91 ± 0·01
	Buffers containing NaCl	5·04 ± 0·02	4·91 ± 0·01
	Buffers containing $BaCl_2$	5·03 ± 0·02	4·90 ± 0·01
pK_1		2·23 ± 0·07	2·43 ± 0·09

Discussion

The results in Tables 1—3 yield mean values of pK_{In} for *m*-, *p*-, and *o*-nitrophenol of 8·35, 7·14, and 7·16 respectively, all probably within ±0·02; the values are in reasonable agreement with those given in earlier literature, *viz.*, for *m*-nitrophenol, 8·30 (Michaelis), 8·30 (Kolthoff), 8·00 (Holleman), 8·28 (Lundén); for *p*-nitrophenol, 7·22 (Michaelis), 7·03 (Kolthoff), 7·16 (Lundén), 7·19 (Holleman); and for *o*-nitrophenol, 7·17 (Holleman), 7·12 (Hantzsch); see Landolt–Börnstein's "Tabellen, etc.," Eg II*b*, p. 1102, and Beilstein's "Handbuch, etc.," VI, 216, 222, 226.

For methyl-red, the results for pK_2 are very consistent even after addition of sodium chloride and barium chloride. The comparatively low accuracy of the pK_1 values arises largely because an indicator concentration suitable for the study of the Red II–yellow stage is too low to secure adequate drum reading differences for change of the Red I to Red II; but since pK_1 was determined only to clarify the interpretation of the pK_2 range, high accuracy was not important. Kolthoff gives 5·05 for pK_2 and 2·60 for pK_1 (*Rec. Trav. chim.*, 1925, **44**, 75).

No colorimetric evidence was found for the existence of a third change-point for methyl-red in the region of pH 9, as claimed by Vlès *et al.* (*Arch. Phys. Biol.*, 1942, **16**, 5) from electrometric measurements. There certainly is, however, another colour change in the very low pH region which appears to have escaped attention hitherto. In 95% sulphuric acid methyl-red undergoes a further change to yellow which can be quantitatively reversed on reducing the acidity, and between this region and pH 0 the absorption in the green is *greater* than can be ascribed to Red I. Although in part this might be explained by the essential alteration of the solvent, it is probable that at least one new form of the indicator is involved. Because of these complications it would be unwise to determine the drum-reading equivalent to Red I by making the solution highly acid.

Procedure for Determination of pH.—It is clear from equation (1) that if, in any solution, the ionic strength is known, and the ratio of the two forms of the indicator can be measured on the absorptiometer, then either pK or pH can be derived if the other is known. The determination of pK_{In} here establishes the validity of the method, and since the nature of the errors involved in determining pH will be exactly similar, the useful range of any indicator is immediately apparent from the reproducibility of pK when solutions of known pH are used.

Now it might appear, from the overlapping of the K_1 and K_2 ranges of methyl-red, that this indicator is not suitable for pH determination. Certainly the initial investigation is complicated by this fact, but, once the essential data have been obtained, application of the indicator to pH determination is simple. The reading c corresponding with the yellow form can be arbitrarily chosen to be, say, 1·00 (or somewhat less) by balancing with the iris diaphragm when the right-hand cell contains a measured proportion of the indicator in dilute aqueous sodium hydroxide, conveniently about 0·01N. Now, although the hypothetical drum-reading b for 100% HIn form is not accessible to direct measurement, this always bears a fixed relation to any readings which *can* be readily reproduced. For convenience, therefore, we may take advantage of the flat minimum in the readings over the intermediate region, as illustrated by the following figures:

p{H⁺}	3·0	3·1	3·2	3·3	3·4	3·5
R	0·217	0·214	0·213	0·213	0·215	0·217

Hence, to reproduce the minimum reading, no accurate buffers are needed; an acetic acid solution roughly diluted to be in the range N/30 to N/70 serves, and the value of b is then calculated directly by the formula: $b = 1{\cdot}016R_{min.} - 0{\cdot}016c$.

There is, however, another feature of indicators of this type which proves especially useful for the present purpose. The intermediate HIn form may be either a zwitterion or an uncharged molecule, and although the latter view seems now to be preferred in the case of methyl-red (Baggesgaard-Rasmussen and Reimers, *Dansk. Tidsskr. Farm.*, 1933, **7**, 225), Kolthoff has pointed out that it does not completely explain the salt-effects (*J. Amer. Chem. Soc.*, 1938, **60**, 2516). It is thus of interest that the complete omission of activity

coefficients from equations (6) and (7), which amounts formally to setting the activity coefficient of HIn equal to that of a univalent ion (cf. Bjerrum, *Z. physikal. Chem.*, 1923, **104**, 147), leads to pK values which, although differing appreciably from those quoted above, are in as good agreement amongst themselves (see Table 6). From a practical point of view it is immaterial that this procedure has little theoretical justification, for, provided that a consistent pK_2 value is used (although merely an empirical value), the p{H$^+$} of any solution can be determined with the same accuracy as with the more acceptable procedure, even in the presence of sodium or barium chloride. It is therefore recommended that the equation which bypasses activity assessments should be used, *viz.*, for methyl red :

$$\text{p}\{\text{H}^+\} = 4{\cdot}91 + \log (c - R) - \log (R - b)$$

in which b must now be consistently determined by the equation :

$$b = 1{\cdot}043R_{\text{min.}} - 0{\cdot}043c.$$

Indicators which are susceptible to this kind of empirical treatment should be selected for development of the method, since the correct assessment of activity effects constitutes its most serious difficulty.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, January 28th*, 1952.]

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738. *The Reaction of Amino-compounds with Sugars. Part I. The Action of Ammonia on* D-*Glucose.*

By L. HOUGH, J. K. N. JONES, and E. L. RICHARDS.

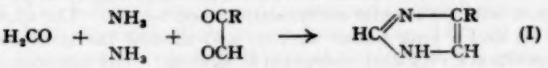
From the complex mixture resulting from the reaction of D-glucose with aqueous ammonia, 4(5)-methylglyoxaline and 2-methyl-5- and 2-methyl-6(?)-(D-*arabo*tetrahydroxybutyl)pyrazine have been isolated and identified.

A MIXTURE of glucose or fructose with aqueous ammonia develops a brown colour (Ling and Nanji, *J. Soc. Chem. Ind.*, 1922, **41**, 151T) and, because of the similarity between this reaction and the " browning " reaction with amino-acids, we have investigated the products. Epimerisation to fructose, mannose, and a ketose (allulose?) occurred rapidly, and then gradually, as the brown colour developed, a very complex mixture resulted. Two strongly coloured zones were observed on the paper chromatogram, one travelling with the solvent front and the other remaining close to the starting line. These brown products have not yet been investigated, attention being confined to the numerous remaining components of the mixture in the hope that they might afford some clue as to the mechanism of formation of the coloured materials.

Fractionation was effected by continuous extraction with chloroform; partition chromatography then gave three fractions, the investigation of two of them being described here.

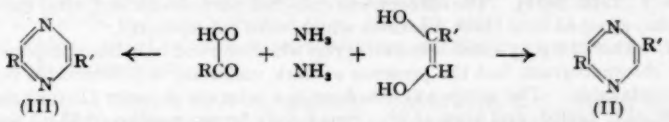
Examination of the first fraction on filter-paper chromatograms revealed the presence of a material that gave a bright red colour when held in ammonia vapour after having been sprayed with diazotised sulphanilic acid (Ames and Mitchell, *J. Amer. Chem. Soc.*, 1952, **74**, 252). This reaction appears to be a characteristic of glyoxalines. On paper chromatograms, the unknown was indistinguishable from 4(5)-methylglyoxaline. Proof of its identity was obtained by the isolation of a crystalline picrate which was identical with authentic 4(5)-methylglyoxaline picrate. Several glyoxalines have been isolated from the reaction between glucose, ammonia, and inorganic bases such as zinc hydroxide, with which glyoxalines form insoluble complexes, as in the preparation of 4(5)-methylglyoxaline (I; R = Me) (Windaus and Knoop, *Ber.*, 1905, **38**, 1166; Windaus, *Ber.*, 1907, **40**, 799). When air is bubbled through the reaction mixture, the main product is 4(5)-hydroxymethylglyoxaline (I; R = CH_2·OH) (Parrod, *Ann. Chim.*, 1933, **19**, 205), and 4(5)-(D-*arabo*-tetrahydroxybutyl)glyoxaline {I; R = [CH(OH)]$_3$·CH_2·OH} is also formed. In order

to account for the formation of 4(5)-methylglyoxaline, Windaus and Knoop postulated fission of the hexose into two molecules of glyceraldehyde, and subsequent conversion of this into methylglyoxal. The latter condenses with ammonia and formaldehyde, which is also formed from fragmentation of hexoses, to form 4(5)-methylglyoxaline. Similarly, hydroxymethylglyoxal and glucose would yield 4(5)-hydroxymethylglyoxaline (I; R = CH_2·OH) and 4(5)-(D-*arabo*tetrahydroxybutyl)glyoxaline respectively.



(I)

From the third fraction of the chloroform extract, fractional crystallisation afforded two isomeric crystalline compounds, $C_9H_{14}O_4N_2$ (*A*, m. p. 201°; *B*, m. p. 170°). Evidence for the presence of a pyrazine nucleus in each was obtained from the ultra-violet absorption curve [principal max. at 2750 A (ε 9540) in water]. Further evidence was obtained by permanganate oxidation of *A* which yields pyrazine-2 : 5-dicarboxylic acid. Both *A* and *B* consumed three mols. of sodium metaperiodate with the simultaneous formation of two mols. of formic acid and one of formaldehyde, thus proving the presence of a tetrahydroxybutyl side chain. Analysis showed the presence of one *C*-methyl group in each. The substance *A* is thus 2-methyl-5-(tetrahydroxybutyl)pyrazine {II; R = Me; R′ = $[CH(OH)]_3$·CH_2·OH}, and *B* is the corresponding 2 : 3- or 2 : 6-compound. The evidence available favours the 2 : 6-configuration {III; R = Me; R′ = $[CH(OH)]_3$·CH_2·OH}. On permanganate oxidation, material was isolated in low yield which sublimed at the temperature and gave the colour with ferrous sulphate expected of pyrazine-2 : 6-dicarboxylic acid and different from those for pyrazine-2 : 3-dicarboxylic acid. As the



(III) (II)

compounds are derived from glucose, the tetrahydroxybutyl side chain would be expected to be D-*arabo* in configuration. This was confirmed by evaluation of the molecular rotations (*A*, $[M]_D^{13}$ −13,360; *B*, $[M]_D^{13}$ −15,820) (cf. Richtmyer and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 1612). Reaction of fructose or glucose with alcoholic ammonia affords fructosazine (2 : 5-bistetrahydroxybutyl)pyrazine {II; R = R′ = $[CH(OH)]_3$·CH_2·OH} (Lobry du Bruyn, *Rec. Trav. chim.*, 1899, **18**, 72; Stolte, *Chem. Zentr.*, 1908, I, 224). It is probable that the pyrazine derivatives we have isolated are formed by the condensation of *aldehydo*-glucose with ammonia and methylglyoxal. This mechanism would give rise to two isomers, the 2 : 6- and the 2 : 5-substituted pyrazine.

Experimental

M. p.s are uncorrected. Analyses for carbon and hydrogen are by Drs. Weiler and Strauss of Oxford, and for nitrogen by W. M. Eno of Bristol.

In the following experiments, sheet-paper partition chromatography was carried out on Whatman No. 1 filter paper by the descending method (Partridge, *Biochem. J.*, 1948, **42**, 238), *n*-butanol–ethanol–water (40 : 11 : 19 v/v) being used, unless otherwise stated, as the mobile phase. After separation, the paper chromatograms were dried, sprayed with one of the following reagents, and, with sprays (*a*)—(*d*), the paper was heated: (*a*) Partridge's ammoniacal silver nitrate reagent (*loc. cit.*); (*b*) *p*-anisidine hydrochloride in butanol–water (Hough, Jones, and Wadman, *J.*, 1950, 1702); (*c*) resorcinol–hydrochloric acid in butanol (Forsyth, *Nature*, 1948, **161**, 239); (*d*) ninhydrin in butanol; (*e*) diazotised sulphanilic acid solution (Ames and Mitchell, *J. Amer. Chem. Soc.*, 1952, **74**, 252). Papers sprayed with (*e*) (not heated) were held over ammonia solution. Solutions were evaporated under reduced pressure unless otherwise stated.

Reaction of D-*Glucose with Ammonia.*—D-Glucose (100 g.) was dissolved in water (1·6 l.) and ammonia (400 ml.; *d* 0·88). The solution was kept in a stoppered vessel (2 l.) at 37° for 2 weeks; the solution gradually became dark brown, but no insoluble material was produced. It was concentrated to 300 ml. and examined qualitatively on paper chromatograms. Spray (*a*) showed

the concentrate to contain at least fifteen components with the following approximate R_G values: * 0·99, 0·85, 0·68, 0·51, 0·49, 0·43, 0·37, 0·33, 0·28, 0·23, 0·17, 0·14, 0·096, 0·078, 0·053, 0·031. The component with R_G 0·99 gave a white spot with reagent (*a*), in contrast to the usual brown spots given by all the other substances, indicating the presence of anionic material. This component with spray (*e*) gave a white spot at the head of an intense red trail. An intense red colour with (*e*) was found to be a characteristic of glyoxalines. When butanol–acetic acid–water (2 : 1 : 1 v/v) was used as the mobile phase, this component moved as a discrete round spot which gave with (*e*) a white centre surrounded by red. The spot of R_G 0·28 gave a yellow colour with (*b*) and a pink colour with (*c*) and showed the same colour reactions and moved to the same position on the chromatogram as allulose. The component of R_G 0·23 gave a brown colour with (*b*) and a pink with (*c*), and moved on the chromatogram to the same position as fructose and mannose. The component of R_G 0·17 gave a brown colour with (*b*) and moved to the same position as glucose. With spray (*d*), a blue streak formed from R_G 0·022 to 0·132 with more intensely blue zones at R_G's 0·033, 0·066, and 0·129. Spray (*e*), as well as showing the component of R_G 0·99, indicated the presence of small quantities of glyoxalines, which appeared as ill-defined elongated spots ranging from the component of R_G 0·99 to the starting line. The course of the reaction was followed by taking samples from the reaction mixture at intervals and examining them on paper chromatograms. Epimerisation took place rapidly, as was indicated by the formation of fructose, mannose, and allulose (?) when the first sample was taken after 16 hours. Other spots had become detectable after 40 hours, and by 100 hours the full pattern had developed.

Fractionation of the Chloroform Extract.—The solution was extracted continuously with chloroform for a week, then evaporated, leaving a thick dark brown syrup (5·9 g.), which was thinned with *n*-butanol, transferred to a column of cellulose, and fractionated by partition chromatography with *n*-butanol, half saturated with water, as the mobile phase (Hough, Jones, and Wadman, *J.*, 1949, 2511). The effluent was collected portionwise and, after examination on chromatograms, grouped into three fractions which were concentrated.

Fraction 1. This (2·5 g.) yielded a brown syrup which showed only one component (R_G 0·99) on the paper chromatogram, but the presence of dark materials, not detectable by the sprays used, was unmistakable. The syrup was dissolved in a mixture of water (20 ml.) and saturated picric acid (30 ml.), boiled, and kept at 0°. Small dark brown needles (0·33 g.) separated and were filtered off (m. p. 153°). Recrystallisation from water gave orange needles (0·2 g.), m. p. 158°, undepressed on admixture with an authentic specimen of 4(5)-methylglyoxaline picrate prepared according to Windaus and Knoop (*Ber.*, 1905, **38**, 1166) (Found: C, 38·6; H, 3·1; N, 22·3. Calc. for $C_{10}H_9O_7N_5$: C, 38·5; H, 2·9; N, 22·5%). Authentic 4(5)-methylglyoxaline behaved in the same way as the component of R_G 0·99 on a paper chromatogram and gave a bright red colour with spray (*e*).

Fraction 2. This (1·4 g.) was a syrup in which the components of R_G 0·85 and 0·68 were detected on a paper chromatogram, along with small amounts of materials giving red colours with spray (*e*). This fraction was not further investigated.

Fraction 3. This (0·4 g.), on evaporation, gave crystals and eventually there remained a mixture of crystals in a light brown syrup. The crystalline material (0·2 g.) was filtered off and identified as 2-*methyl*-5-(D-arabo*tetrahydroxybutyl*)*pyrazine* (II), m. p. 196°, raised to 201° on recrystallising twice from absolute ethanol, $[\alpha]_D^{13}$ −62·4° (*c*, 0·42 in water) (Found: C, 50·4; H, 6·4; N, 13·1; *C*-Me, 6·8. $C_9H_{14}O_4N_2$ requires C, 50·5; H, 6·54; N, 13·1; *C*-Me, 7·1%). The optical rotation varies appreciably with the temperature. On the paper chromatogram, this material reduced spray (*a*) to give a brown spot (R_G 0·49), but no colour was produced with spray (*b*) or (*e*).

Periodate Oxidation of 2-*Methyl*-5-(D-arabo*tetrahydroxybutyl*)*pyrazine* (II).—The pyrazine (5 mg.) in water (5 ml.) was treated with sodium metaperiodate (0·2M; 1 ml.) for 3 hours at room temperature. Addition of neutral sodium arsenite (5 c.c., 0·1N), followed by back-titration with 0·01N-iodine (26 c.c.), showed that 2·8 moles of periodate were consumed per mole of (II). A control determination was carried out on 1 ml. of periodate (0·2M) and 5 c.c. of arsenite solution (0·1N), and required 13 ml. of 0·01N-iodine. Similar oxidation of another portion (5·9 mg.) with sodium metaperiodate (0·2M; 1 ml.) gave formic acid equivalent to 2·45 c.c. of 0·02N-sodium hydroxide, corresponding to 1·9 moles of formic acid per mole of (II). Similar oxidation of another portion (9·8 mg.) gave formaldehyde, identified as the dimedone derivative (12·7 mg.), m. p. 186° (Bell, *J.*, 1948, 992), equivalent to 0·78 mole of formaldehyde per mole of (II).

* 2 : 3 : 4 : 6-Tetramethyl glucose (R_G 1·0) is used as the reference substance (Hirst, Hough, and Jones, *J.*, 1949, 928).

Pyrazine-2 : 5-dicarboxylic Acid.—2-Methyl-5-(D-*arabo*tetrahydroxybutyl)pyrazine (II) (0·2 g.) was heated in 2% potassium permanganate solution (75 ml.) under reflux for 18 hours. The solution was filtered, concentrated to 15 c.c., and acidified with dilute nitric acid. The white precipitate (19 mg.) was dissolved in dilute aqueous ammonia, filtered, and reprecipitated (14 mg.) by dilute nitric acid. The dicarboxylic acid sublimed at 265—270° and gave a violet-blue colour with ferrous sulphate solution (Found: C, 43·1; H, 2·54; N, 16·6. Calc. for $C_6H_4O_4N_2$: C, 42·9; H, 2·38; N, 16·7%). An *X*-ray powder photograph of the crystals was identical with that of an authentic specimen of pyrazine-2 : 5-dicarboxylic acid obtained by the oxidation of 2 : 5-dimethylpyrazine (Gabriel and Pinkus, *Ber.*, 1893, **26**, 2197), the best results being obtained by dissolving 2 : 5-dimethylpyrazine (0·41 g.) in 2% potassium permanganate solution (150 ml.) and treating it as above (yield, 0·165 g.).

2-Methyl-6-(D-arabo*tetrahydroxybutyl)pyrazine* (III).—The mother-liquor, after the removal of (II), was evaporated further to about a quarter of its volume. Needles gradually separated (0·1 g.; m. p. 166°) which were recrystallised from absolute ethanol, then having m. p. 170°, $[\alpha]_D^{13}$ −74° (*c*, 0·425 in water) (Found: C, 50·5; H, 6·22; N, 13·2; *C*-Me, 7·7. $C_9H_{14}O_4N_2$ requires C, 50·5; H, 6·54; N, 13·1; *C*-Me, 7·1%). The optical rotation of this compound also exhibits considerable variance with temperature. On a paper chromatogram, this material gave a discrete brown spot (R_G 0·51) with spray (*a*).

Periodate oxidation. By the methods described above, it was found that 3·08 moles of periodate were consumed per mole of (III), with the formation of 2 moles of formic acid and 0·85 mole of formaldehyde.

Permanganate oxidation. The pyrazine (III) (0·2 g.) was heated with 2% potassium permanganate solution (75 ml.) as described above for (II). On concentration and acidification a small amount (4 mg.) of a pale yellow material separated. This was isolated on the filter; it sublimed at 220° and gave a reddish-blue colour with ferrous sulphate solution, different from the violet-blue colour given by pyrazine-2 : 3-dicarboxylic acid [prepared by the oxidation of quinoxaline by Gabriel and Sonn's method (*Ber.*, 1907, **40**, 4850)]. The m. p.s of the pyrazine-dicarboxylic acids in sealed tubes were unsatisfactory and the temperature of sublimation was found to be more characteristic.

We thank Mr. G. I. Gregory for *X*-ray analyses. One of us (E. L. R.) thanks the New Zealand Defence Science authorities for the award which enabled the work described in this paper to be undertaken.

THE UNIVERSITY, BRISTOL. [*Received, July 4th*, 1952.]

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739. *Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part XI.* The Oxidation Potentials of Naphthidine, 3 : 3′-Dimethylnaphthidine, and their Sulphonic Acids.*

By R. BELCHER, A. J. NUTTEN, and W. I. STEPHEN.

The transition potentials of naphthidine, naphthidinesulphonic acid, 3 : 3′-dimethylnaphthidine, and 3 : 3′-dimethylnaphthidinedisulphonic acid have been determined by comparison with the molar electrode potentials of the ferrous–ferric and dichromate–chromic systems, in various concentrations of acid. The values obtained are 0·800, 0·840, 0·706, and 0·800 volt respectively in molar sulphuric acid.

THE oxidation potentials of the indicators naphthidine, naphthidinesulphonic acid, 3 : 3′-dimethylnaphthidine, and 3 : 3′-dimethylnaphthidinedisulphonic acid, the uses of which we have described in earlier papers of this series, have been determined by examining their behaviour on oxidation with ceric sulphate and potassium dichromate.

Initially, it was intended to obtain the oxidation potentials of these indicators by a method similar to that used by Crawford and Bishop (*J. Royal Tech. Coll. Glasgow*, 1950, **5**, 52) who studied the oxidation of *o*-dianisidine by direct titration with ceric sulphate and obtained from the potentiometric titration curves the potentials corresponding to 50% oxidation of the indicator. These workers have pointed out the limitations of this method,

* Part X, *J.*, 1952, 2438.

the most important being the assumption of a completely reversible system involving a two-electron change in the indicator oxidation reaction. Diamines of the benzidine series do not undergo direct oxidation to diquinoneimines (cf. Fieser, *J. Amer. Chem. Soc.*, 1930, **52**, 4915), several other reactions occurring between the oxidised and the reduced diamine which lead to irreversible formation of condensed reaction products. However, Crawford and Bishop claim that their values for the mid-point potentials are reasonably accurate and any interference from side reactions is reduced to a minimum at the critical stage of the titration.

The diamines of the dinaphthyl series have proved to be unsuited to this procedure; naphthidine and its sulphonic acid are too readily transformed, irreversibly, by oxidants to products possessing no indicator properties, rendering any attempts to measure their potentials useless. 3 : 3′-Dimethylnaphthidine and its disulphonic acid give more stable oxidation products and it is possible to obtain titration curves corresponding to 95% oxidation of the free base and 75—80% oxidation of the disulphonic acid. The mid-point of the titration curves has to be read at the theoretical volume of ceric sulphate solution required to oxidise 50% of the indicator. Values of the potentials for these two indicators, referred to the molar hydrogen electrode, are listed below for several values of pH.

The limitations of this method make these figures unreliable and of little practical or theoretical significance. The real value of an indicator oxidation potential is its use as a guide in evaluating the merits of the indicator in certain redox reactions in which it may function. In view of this, it was decided to examine the behaviour of all four indicators in actual redox titrations and to note the potentials at which these indicators first showed change of colour under varying concentration of acid.

Oxidation potentials (mv) *by direct titration with* Ce^{4+}. *Temp.* 18°.

3 : 3′-Dimethylnaphthidine.

E_h (ref. standard H_2 electrode)	776	755	726	714	711
pH	0	0·28	0·50	0·79	1·00

3 : 3′-Dimethylnaphthidinedisulphonic acid.

E_h (ref. standard H_2 electrode)	838	796	802	806	784
pH	0	0·28	0·50	0·79	1·00

Before an examination of these potentiometric transitition potentials could be made, reference potentials for the single-electrode systems, Fe^{3+}–Fe^{2+} and $Cr_2O_7^{2-}$–Cr^{3+}, were required which would prove to be standards of potential under different conditions. Since, in this respect, the standard oxidation potentials are useless, the concept of molar potentials [identical in every respect except name with " formal " potentials (Swift, " A System of Chemical Analysis," Prentice-Hall, 1939, pp. 39, 40, and 540)] was used. Practical values are thus obtained for the redox potentials which bear little resemblance to the idealised reaction constants—the standard oxidation potentials. These molar potentials are the values for redox reactions in solutions of known molar strength. These standard and molar oxidation potentials differ because of the conditions under which they are determined; the standard oxidation potentials correspond to values obtained in solutions conforming to the conditions of the thermodynamical standard state, while the molar potentials do not adhere strictly to the prerequisites of these conditions. These potentials would be interconvertible if adequate data were available for hydrolysis constants, activity coefficients, and complex-ion dissociation constants in the relatively concentrated solutions in which these molar potentials are measured. Since these data are lacking, it is preferable to use the experimentally measured molar potentials.

The molar potentials of the single-electrode systems, Fe^{3+}–Fe^{2+} and $Cr_2O_7^{2-}$–Cr^{3+}, were determined in various concentrations of sulphuric acid by titrating potentiometrically known amounts of standard ferrous sulphate solution with standard potassium dichromate solution. From the titration curves obtained, the values for the half-cell reactions

$$Fe^{2+} \rightleftharpoons Fe^{3+} + \varepsilon$$

and

$$Cr_2O_7^{2-} + 14H^+ + 6\varepsilon \rightleftharpoons 2Cr^{3+} + 7H_2O$$

were read. These values, referred to the standard hydrogen electrode, are listed below.

Molar redox potentials (mv) *of the systems* $Cr_2O_7^{2-}$–Cr^{3+} *and* Fe^{2+}–Fe^{3+} *in various concentrations of sulphuric acid, at* 18°.

Acid, M	0·1	0·5	1·0	2·0	4·0	8·0
Fe^{3+}–Fe^{3+} system	680	682	680	684	688	646
$Cr_2O_7^{2-}$–Cr^{3+} system	926	1075	1098	1106	1142	1336

These values are in excellent agreement with the " formal " potentials recently determined by Smith (*Anal. Chem.*, 1951, **23**, 925). When compared with the standard redox potentials $E°_{Fe^{3+}-Fe^{2+}} = 771$ and $E°_{Cr_2O_7-Cr^{3+}} = 1360$ mv, listed in several books, it is seen that little agreement exists. From the standard potentials it would seem that only indicators possessing a high transition potential would be suitable in ferrous–dichromate titrations, yet the recorded potentials of diphenylbenzidine, diphenylamine, and the sulphonic acids of both these substances lie in the range 760—860 mv. These potentials are sufficiently close to the standard ferrous–ferric potential, which corresponds to the oxidation of only 50% of the ferrous ions, to warrant further explanation. This situation arises because it is customary to compare the experimentally determined transition potentials of redox indicators with the standard potentials of the redox systems involved in the titrations, instead of comparing them with the experimentally measured molar potentials. Kolthoff and Sandell (" Quantitative Inorganic Analysis," The MacMillan Co., 1950, p. 491) state that the action of a redox indicator does not generally depend upon the specific nature of the oxidant or reductant being titrated, but upon the relative positions of the oxidation potentials of the indicator and the titrated system. To this, Smith and Richter (" Phenanthroline and Substituted Phenanthroline Indicators," G. F. Smith Chemical Co., 1944, p. 44) have added that the transition point for redox indicators often occurs at different potential levels, depending upon the concentration and nature of the solution being studied; before predicting the behaviour of the reactants involved, some practical distinction should be made between standard and molar potentials.

Thus, in M-sulphuric acid, the molar potentials $E°'_{Fe^{3+}-Fe^{2+}} = 680$ mv and $E°'_{Cr_2O_7^{2-}-Cr^{3+}} = 1098$ mv justify the use of diphenylamine and related indicators in ferrous–dichromate titrations. The potential of the ferrous–ferric system can, however, be lowered by the complexing action of phosphoric acid and falls to 610 mv in a solution M with respect to sulphuric acid and 0·5M with respect to phosphoric acid, although no data are available for the corresponding standard potential of this system. If the value for the ferrous–ferric system (771 mv) was to be assumed as obtaining in an actual titration in M-acid, then ferric ions would be expected to oxidise the indicator. This does not occur; hence the actual potential involved is much lower.

The transition potentials of the dinaphthyl-diamines and their sulphonic acids were determined by observing the potential at which each indicator first showed change of colour in the titration of ferrous ions with dichromate. By a suitable procedure described below, the transition interval could be narrowed by reversal of the colour change. Naphthidine, naphthidinesulphonic acid, and 3 : 3′-dimethylnaphthidinedisulphonic acid all gave sharp transition potentials because the transition interval could readily be narrowed by only two or three reversals of the colour. On the other hand, 3 : 3′-dimethylnaphthidine behaved sluggishly, making it difficult to narrow the potential to a definite figure. This is in accord with our previous observation (*J.*, 1952, 1269) that 3 : 3′-dimethylnaphthidine has little application as an indicator in titrations with dichromate. The approximate transition potential of this indicator was, however, obtained by the general procedure.

It was found that, under the experimental conditions employed, both naphithdine and its sulphonic acid behaved reversibly over a sufficient number of changes, although the colour of the oxidised indicator appeared to become less intense and assumed a duller shade as the number of reversals of the colour was increased. Naphthidinesulphonic acid itself is not very stable in its oxidised form as is shown by the rapid disappearance of the oxidised indicator from solution, which in turn, assumes a pale brownish-yellow colour.

The transition potentials for each indicator over a range of acid concentrations are listed below. For comparison, the values for barium diphenylaminesulphonate were determined and these are included. Sarver and Kolthoff (*J. Amer. Chem. Soc.*, 1931, **53**, 2902) record a value of 840 mv for the transition potential of this indicator in M-acid.

Transition potentials (mv, ***referred to the hydrogen electrode***) ***of the dinaphthyldiamines and barium diphenylaminesulphonate in various concentrations of sulphuric acid at*** 18°.

	Naphthidine.						Naphthidinesulphonic acid.					
Acid concn., M ...	0·1	0·5	1·0	2·0	4·0	8·0	0·1	0·5	1·0	2·0	4·0	8·0
E.M.F.	810	804	800	780	755	740	842	840	840	820	810	792

	3 : 3′-Dimethylnaphthidine.						3 : 3′-Dimethylnaphthidinedisulphonic acid.					
Acid concn., M ...	0·1	0·5	1·0	2·0	4·0	8·0	0·1	0·5	1·0	2·0	4·0	8·0
E.M.F.	710	710	706	706	710	700	816	810	800	785	766	750

	Barium diphenylaminesulphonate.					
Acid concn., M	0·1	0·5	1·0	2·0	4·0	8·0
E.M.F.	853	850	830	800	770	710

From these results it appears at first sight that naphthidinesulphonic acid is a comparable indicator to barium diphenylaminesulphonate, and indeed at high acid concentrations should be superior since it shows less of a decrease in potential as the acidity is increased. However, it possesses the inherent disadvantages of reacting somewhat less rapidly with oxidant at the end-point and of being more susceptible to destruction by a slight excess of oxidant. In practice, these disadvantages are not serious. Consideration of the structure of the indicator molecules leads to two conclusions. Sulphonation, as with diphenylamine (transition potential, 760 mv), leads to an increase in oxidation potential. The presence of methyl groups in the naphthidine nucleus reduces the potential considerably.

The results obtained from the direct titration of the indicators with ceric sulphate bear only qualitative agreement with the standard potentials, being, in each instance, higher by some 40—60 mv. For practical purposes it is evident that the direct titration procedure for evaluating the oxidation potentials is of little value.

Experimental

Apparatus.—All potential measurements were obtained by using a Marconi Instruments pH meter (mains type) as a valve potentiometer. A bright platinum indicating electrode was used in conjunction with a saturated calomel reference electrode. The titration medium was stirred by means of a magnet rotating in the liquid, and activated by an external rotating magnet.

Solutions Required.—Ceric sulphate, 0·01N. Prepared by appropriate dilution of 0·1N-ceric sulphate solution, whose concentration was accurately known by titration against standard ferrous solution with 1 : 10-phenanthroline–ferrous complex as indicator. The diluted solution was standardised by a similar procedure.

Potassium dichromate, 0·1, 0·01, and 0·002N. The concentrated solution was prepared by dissolving 4·9035 g. of "AnalaR" potassium dichromate in 1 l. of sulphuric acid of known concentration. Solutions of 0·1N-dichromate were prepared in 0·1, 0·5, 1·0, 2·0, 4·0, and 8·0M-sulphuric acid. The weaker solutions were prepared by dilution with acid of the appropriate concentration.

Ferrous sulphate, 0·1, 0·01, and 0·002N. The 0·1N-solution was prepared by dissolving 27·803 g. of "AnalaR" ferrous sulphate heptahydrate in 1 l. of sulphuric acid of known molarity. Solutions of 0·1N-ferrous sulphate were prepared in 0·1, 0·5, 1·0, 2·0, and 4·0M-sulphuric acid. It was impossible to dissolve this amount of ferrous sulphate in 8M-sulphuric acid, so, after prolonged shaking, the undissolved ferrous sulphate was filtered off and the solution retained. The weaker solutions were prepared by dilution with the appropriate acid.

Sulphuric acid, 0·1, 0·5, 1·0, 2·0, 4·0, and 8·0M. These solutions were prepared by dissolving the requisite weight of pure sulphuric acid in water; 5—6 l. of each strength were prepared for use in diluting the ferrous, dichromate, and titration solutions.

Indicators. For the direct titration procedure, 3 : 3′-dimethylnaphthidine and its disulphonic acid sulphate were used in known amounts. In the potential measurements, 0·2% solutions of all four indicators were used (*J.*, 1952, 1273).

Procedure.—(A) *Direct titration of* 3 : 3′*-dimethylnaphthidine and its disulphonic acid with ceric sulphate.* 20 mg. amounts of each indicator were titrated potentiometrically with 0·01N-ceric sulphate solution by using the apparatus described above. The indicators were suspended in solutions containing sulphuric acid or sulphuric acid–sodium acetate mixtures, of known pH. Near the mid-point of the titration several readings were taken after the attainment of equilibrium, and the change in potential was plotted against the volume of 0·01N-ceric solution for each

titration. The mid-point potentials were obtained from the volume of ceric solution theoretically equivalent to the amount of indicator added (12·80 ml. for 20 mg. of 3 : 3′-dimethylnaphthidine, and 7·02 ml. for 20 mg. of 3 : 3′-dimethylnaphthidinedisulphonic acid sulphate).

(B) *Determination of the molar potentials of the* Fe^{2+}–Fe^{3+} *and* $Cr_2O_7^{2-}$–Cr^{3+} *systems.* The single-electrode potentials were determined by pipetting 25·00 ml. of ferrous solution of known acid content into a beaker and diluting it to about 100 ml. with acid of identical strength. The initial potential of the system was noted, and the ferrous ions then oxidised by addition of 0·1N-potassium dichromate in an identical concentration of acid. Potential readings were taken at frequent intervals during the addition of dichromate, to the stage where 100% excess had been added. From the potentiometric titration curves, the values for the molar potentials of both single-electrode systems involved, referred to the saturated calomel electrode, were thus obtained, for each concentration of sulphuric acid.

(C) *Determination of the transition potentials of the dinaphthyldiamines and their sulphonic acids.* The transition potential of each indicator was determined by titrating known amounts of ferrous sulphate solution with 0·1N-dichromate, as described in section (B). In each titration 2 drops of 0·2% indicator solution were added. Potential readings were taken at frequent intervals, except near the mid-point of the titration where several readings were obtained to check the molar potential of the ferrous–ferric system. About 0·25 ml. from the theoretical end-point, the 0·1N-dichromate was replaced by a 0·01N-solution which was added dropwise in order to raise the potential slowly. The transition potential was obtained when the indicator showed the first change of colour as compared with a standard solution containing identical amounts of acid, ferrous solution, and indicator, which had been titrated to within 0·5 ml. of the calculated end-point volume. The solution under investigation was then over-titrated, and the colour change reversed by the dropwise addition of 0·01N-ferrous solution. The colour of oxidised indicator was brought back by titration with 0·002N-dichromate. A single reversal with 0·002N-solutions served to decrease the transition interval by not more than 3—4 mv, thus giving an accurate value for the transition potential. This procedure was applied to the four dinaphthyl-type indicators, and also to barium diphenylaminesulphonate, for each of the six concentrations of sulphuric acid.

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740. 4-*Aminosalicylic Acid and its Derivatives. Part III.** *Some Reactions of 2-Acetoxy-4-nitrobenzoyl Chloride and the Synthesis of some Aryl Esters of 4-Aminosalicylic Acid.*

By P. R. Banerjea, D. J. Drain, K. H. Overton, and D. E. Seymour.

Further derivatives of 4-aminosalicylic acid have been made for examination as antituberculous compounds. A series of substituted amides and aryl esters of 4-aminosalicylic acid has been obtained from 4-nitrosalicylic acid.

Use of 4-aminosalicylic acid in the treatment of tuberculosis led to the preparation of many of its derivatives (*e.g.*, Doub, Schaefer, Bambas, and Walker, *J. Amer. Chem. Soc.*, 1951, **73**, 903; Drain, Martin, Mitchell, Seymour, and Spring, *J.*, 1949, 1498; Hirt and Hurni, *Helv. Chim. Acta*, 1949, **32**, 378; Rosdahl, *Svensk Kem. Tidskr.*, 1948, **60**, 12). This paper records a further series of derivatives, the pharmacological and tuberculostatic properties of which have been or will be published elsewhere (cf. Drain, Goodacre, and Seymour, *J. Pharm. Pharmacol*, 1949, **1**, 784).

Treatment of 2-acetoxy-4-nitrobenzoic acid with thionyl chloride in benzene gave the chloride which by reaction with the amine, followed by deacetylation and reduction, afforded a series of amides. The chloride was converted into 4-amino-2-hydroxyphenylacetic acid by Wolff rearrangement of the intermediate diazo-ketone.

The report by Friere (*Compt. rend.*, 1950, **231**, 728) that phenyl 4-aminosalicylate is a more active tuberculostatic agent than either the acid or chloramphenicol prompted us to synthesise a series of aryl esters. These were obtained by reaction of 4-nitrosalicylic acid

* Part II, *J.*, 1950, 1139.

with the phenol in the presence of phosphoryl chloride, and subsequent reduction by hydrogen in the presence of Adams's catalyst or by zinc and ammonium chloride.

4-Amino-3 : 5-di-iodosalicylic acid was obtained from the amino-acid by iodine and hydrogen peroxide or by treatment of methyl 4-aminosalicylate with iodine chloride followed by hydrolysis.

4-Benzylsulphonamidosalicylic acid was prepared from methyl 4-aminosalicylate by standard methods.

Experimental

2-Acetoxy-4-nitrobenzoyl Chloride.—2-Acetoxy-4-nitrobenzoic acid (4·5 g.). thionyl chloride (9 ml.), and benzene (30 ml.) were refluxed for 30 minutes and concentrated under reduced pressure to give a pale yellow syrup which crystallised. The chloride separated from benzene–light petroleum (b. p. 40—60°) in pale yellow needles, m. p. 56°. Doub, Schaefer, Bambas, and Walker (*J. Amer. Chem. Soc.*, 1951, **73**, 903) give m. p. 57°.

2-Acetoxy-4-nitrobenzo-p-*toluidide.*—2-Acetoxy-4-nitrobenzoyl chloride (from 1·5 g. of acid) was heated with *p*-toluidine (1·5 g.) in ether (50 ml.) under reflux for 30 minutes. The solution was extracted with dilute hydrochloric acid, and the ethereal layer dried ($MgSO_4$) and evaporated. *2-Acetoxy-4-nitrobenzo*-p-*toluidide* separated from ethanol in pale yellow needles, m. p. 131° (Found : C, 60·4; H, 4·3; N, 8·9. $C_{16}H_{14}O_5N_2$ requires C, 61·1; H, 4·45; N, 8·9%).

2-Hydroxy-4-nitrobenzo-p-*toluidide.*—2-Acetoxy-4-nitrobenzo-*p*-toluidide (0·7 g.) was heated under reflux for 30 minutes with methanol (50 ml.) containing 20% aqueous potassium hydroxide (10 ml.) and the mixture poured into ice-water (200 ml.) and 20% hydrochloric acid (15 ml.). The precipitated *2-hydroxy-4-nitrobenzo*-p-*toluidide* (0·5 g.) separated from dioxan in pale yellow needles, m. p. 251° (Found : C, 61·6; H, 4·4; N, 10·2. $C_{14}H_{12}O_4N_2$ requires C, 61·75; H, 4·4; N, 10·3%).

Similarly, *2-hydroxy-4-nitrobenzanilide* was obtained (without purification of the intermediate acetoxy-compound) as pale yellow needles (from aqueous dioxan), m. p. 238° (Found : C, 60·8; H, 3·8; N, 10·8. Calc. for $C_{13}H_{10}O_4N_2$: C, 60·45; H, 3·9; N, 10·85%). Doub *et al.* (*loc. cit.*) report m. p. 234—235°.

4-Amino-2-hydroxybenzo-p-*toluidide.*—The nitro-toluidide (1·45 g.) in 50% aqueous methanol (100 ml.) containing 5N-sodium hydroxide (1·1 ml.) was hydrogenated over Adams's catalyst at room temperature and pressure until absorption ceased. The catalyst was removed, the filtrate neutralised with acetic acid, and the product (0·9 g.) collected.

4-Amino-2-hydroxybenzo-p-*toluidide* separated from aqueous methanol as pale cream-coloured needles, m. p. 172° (Found : C, 69·3; H, 5·9; N, 11·6. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8; N, 11·6%).

Similarly, *4-amino-2-hydroxybenzanilide* was obtained as colourless needles (from aqueous methanol), m. p. 151° (Found : C, 68·4; H, 5·3; N, 12·4. Calc. for $C_{13}H_{12}O_2N_2$: C, 68·4; H, 5·3; N, 12·3%). Doub *et al.* (*loc. cit.*) report m. p. 144—145°.

2-Hydroxy-4-nitrohippuric Acid.—2-Acetoxy-4-nitrobenzoyl chloride (from 4·5 g. of acid) in dry benzene (30 ml.) was added dropwise during 30 minutes to a vigorously stirred solution of glycine (1·5 g.) in 20% aqueous sodium hydroxide (4 ml.) and 10% aqueous sodium hydrogen carbonate (80 ml.). After 2 hours the mixture was diluted with water (100 ml.) and extracted with ether (50 ml.). The aqueous layer was acidified with hydrochloric acid, to yield a pale yellow solid (2·78 g.) which was extracted for 15 minutes with boiling ether (25 ml.) to remove 4-nitrosalicylic acid. The insoluble residue (1·28 g.) separated from dilute ethanol as a pale yellow microcrystalline powder, m. p. 203—205° (Found : C, 45·1; H, 3·35; N, 11·8. Calc. for $C_9H_8O_6N_2$: C, 45·0; H, 3·3; N, 11·7%). Doub *et al.* (*loc. cit.*) report m. p. 211°.

Similarly prepared was *2-hydroxy-4-nitrobenzoyl*-DL-*alanine* which separated from aqueous ethanol in pale yellow crystals, m. p. 226—227° (Found : C, 47·4; H, 4·0; N, 11·4. $C_{10}H_{10}O_6N_2$ requires C, 47·2; H, 3·9; N, 11·0%), and *2-hydroxy-4-nitrobenzoyl*-DL-*aspartic acid*, a pale yellow microcrystalline powder (from aqueous ethanol), m. p. 203—205° (Found : C, 44·5; H, 3·4; N, 9·4. $C_{11}H_{10}O_8N_2$ requires C, 44·3; H, 3·35; N, 9·4%).

4-Amino-2-hydroxyhippuric Acid.—2-Hydroxy-4-nitrohippuric acid (2·4 g.) in 50% ethanol (100 ml.) containing sodium hydrogen carbonate (0·84 g.) was hydrogenated over Adams's catalyst at atmospheric pressure and temperature until absorption ceased. Removal of catalyst followed by addition of hydrochloric acid (9·7 ml. of 1·03N) and evaporation to dryness yielded a solid which was triturated with water to remove sodium chloride. From the residue (1·3 g.), *4-amino-2-hydroxyhippuric acid* separated as colourless crystals, m. p. 170—175°

(decomp.) (from water) (Found: C, 51·4; H, 4·7; N, 13·2. $C_9H_{10}O_4N_2$ requires C, 51·4; H, 4·75; N, 13·3%).

Similarly prepared were *4-amino-2-hydroxybenzoyl-*DL*-alanine*, pale brown (from water), m. p. 168—170° (decomp.) (Found: C, 53·4; H, 5·5; N, 12·5. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%), and *4-amino-2-hydroxybenzoyl-*DL*-aspartic acid*, pale brown (from water), m. p. 204° (decomp.) (Found: C, 49·1; H, 4·5; N, 10·5. $C_{11}H_{12}O_6N_2$ requires C, 49·2; H, 4·5; N, 10·4%).

2-Acetoxy-4-nitrophenyl Diazomethyl Ketone.—2-Acetoxy-4-nitrobenzoyl chloride (from 9 g. of acid) in dry ether was added gradually to an ethereal solution of diazomethane (from 17 g. of methyl-*N*-nitrosourea) with swirling at 0°. The solution was kept for 2 hours at 0°, then overnight at room temperature. Removal of the ether yielded the diazo-ketone (7·9 g.), m. p. 90—94°, sufficiently pure for Wolff rearrangement. A sample recrystallised 3 times from benzene–light petroleum yielded pale yellow prisms of *diazo-ketone*, m. p. 110° (decomp.) (Found: C, 48·1; H, 2·9; N, 16·6. $C_{10}H_7O_5N_3$ requires C, 48·2; H, 2·8; N, 16·85%).

Methyl 2-Acetoxy-4-nitrophenylacetate.—2-Acetoxy-4-nitrophenyl diazomethyl ketone (6·4 g.) in methanol (100 ml.) was warmed to 60° and a methanolic suspension of silver oxide (from 20 ml. of 10% aqueous silver nitrate) added in portions during 30 minutes. The mixture was refluxed for 30 minutes and filtered whilst hot (charcoal). Evaporation under reduced pressure to 25 ml. yielded colourless needles (2·9 g.); a further 0·65 g. was obtained by evaporating the mother-liquors to dryness and triturating the residue with methanol. *Methyl 2-acetoxy-4-nitrophenylacetate* separated from methanol in colourless feathery needles, m. p. 85·5° (Found: C, 52·1; H, 4·45; N, 5·55. $C_{11}H_{11}O_6N$ requires C, 52·2; H, 4·35; N, 5·5%).

The ester (3·55 g.) was heated under reflux for 45 minutes with glacial acetic acid (12 ml.) and hydrochloric acid (18 ml.). The hot solution was filtered (charcoal) and diluted with water (60 ml.). On cooling, the crude acid (2·1 g.) separated, and the mother-liquors yielded a further 0·6 g. on ether-extraction. 2-Hydroxy-4-nitrophenylacetic acid separated from water in pale yellow needles as a *monohydrate*, m. p. 147—148° (Found: C, 44·8; H, 4·2; N, 6·35. $C_8H_7O_5,H_2O$ requires C, 44·7; H, 4·2; N, 6·5%).

4-Amino-2-hydroxyphenylacetic Acid.—The nitro-acid (2·1 g.) in methanol (50 ml.), hydrogenated at atmospheric temperature and pressure over Adams's catalyst, gave *4-amino-2-hydroxyphenylacetic acid* (1·4 g.) as pale yellow prisms (from water), m. p. 188—189° (Found: C, 57·5; H, 5·4; N, 8·1. $C_8H_9O_3N$ requires C, 57·5; H, 5·4; N, 8·4%).

4-(2-Acetoxy-4-nitrobenzamido)salicylic Acid.—2-Acetoxy-4-nitrobenzoyl chloride (from 5·62 g. of acid) in dry benzene (100 ml.) was added dropwise with stirring to a suspension of 4-aminosalicylic acid (7·64 g.) in dry ether (250 ml.). After 2 hours the solvents were removed under reduced pressure and the residue boiled with alcohol (200 ml.) and filtered from 4-aminosalicylic acid hydrochloride. The filtrate was concentrated and on refrigeration the product (6·7 g.) separated. *4-(2-Acetoxy-4-nitrobenzamido)salicylic acid* crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as clusters of pale yellow needles, m. p. 240—242° (decomp.) (Found: C, 53·1; H, 3·35; N, 7·6. $C_{16}H_{12}O_8N_2$ requires C, 53·35; H, 3·35; N, 7·8%).

This (2·0 g.) in alcohol (150 ml.) was kept at room temperature for 5 minutes with alcoholic potassium hydroxide (50 ml. of 4%). On acidification, and dilution with water (200 ml.), the product separated as a yellow amorphous solid (1·8 g.). Reprecipitation from aqueous alkali gave a pale yellow jelly which on dilution with two volumes of alcohol gave a clear solution from which *4-(2-hydroxy-4-nitrobenzamido)salicylic acid* separated as small yellow needles, m. p. 279—280° (decomp.) (Found: C, 52·8; H, 3·2; N, 8·4. $C_{14}H_{10}O_7N_2$ requires C, 52·85; H, 3·15; N, 8·8%).

4-(4-Amino-2-hydroxybenzamido)salicylic Acid.—4-(2-Hydroxy-4-nitrobenzamido)salicylic acid (1·4 g.) in water containing sodium hydrogen carbonate (1·1 g.) was hydrogenated at atmospheric temperature and pressure over Adams's catalyst, the theoretical amount of hydrogen being absorbed in about 20 minutes. After removal of the catalyst the filtrate was acidified with acetic acid. The product was a yellow amorphous solid (1·2 g.). Two recrystallisations from aqueous acetone gave the *amino-acid* as yellow needles, m. p. 251° (decomp.) (Found: C, 58·8; H, 4·85; N, 9·3. $C_{14}H_{12}O_5N_2$ requires C, 58·4; H, 4·2; N, 9·7%).

Phenyl 4-nitrosalicylate.—4-Nitrosalicylic acid (18·3 g., 0·1 mole), phenol (9·4 g., 0·1 mole), and phosphorus oxychloride (6·16 g., 0·04 mole) were heated at 120° for 3 hours. After cooling, the mixture was ground with water, then with sodium hydrogen carbonate solution. The solid was dried and crystallised from acetone, from which *phenyl 4-nitrosalicylate* (13·1 g.) separated as pale yellow prisms, m. p. 148—150° (Found: C, 60·4; H, 3·5; N, 5·8. $C_{13}H_9O_4N$ requires C, 60·2; H, 3·7; N, 5·8%).

Similarly prepared were o-, pale yellow prisms (from 50% alcohol), m. p. 94° (Found: C, 61·7; H, 4·04; N, 5·2. $C_{14}H_{11}O_5N$ requires C, 61·5; H, 4·0; N, 5·1%), m-, pale yellow needles (from acetone), m. p. 94—95° (Found: C, 61·5; H, 4·2; N, 5·3%), and p-*tolyl*, pale yellow needles (from 50% alcohol), m. p. 122° (Found: C, 61·2; H, 4·2; N, 6·2%), β-*naphthyl*, pale yellow crystals (from ethyl acetate), m. p. 189—190° (Found: C, 66·1; H, 3·65; N, 4·7. $C_{17}H_{11}O_5N$ requires C, 66·0; H, 3·55; N, 4·5%), m-, pale yellow needles (from aqueous acetone), m. p. 166·5—167° (Found: C, 51·35; H, 2·55; N, 9·3. $C_{13}H_8O_7N_2$ requires C, 51·30; H, 2·65; N, 9·2%), and p-*nitrophenyl* 4-*nitrosalicylate*, yellow prismatic needles (from acetone), m. p. 154—154·5° (Found: C, 51·75; H, 2·75; N, 9·4%).

Phenyl 4-*aminosalicylate*.—(*a*) Phenyl 4-nitrosalicylate (2·5 g.) in ethyl acetate (250 ml.) was shaken with Adams's catalyst under hydrogen at atmospheric pressure until absorption ceased. After removal of the catalyst the solution was evaporated to dryness under reduced pressure and the residue crystallised from alcohol, from which *phenyl* 4-*aminosalicylate* separated in pale cream-coloured needles, m. p. 145—146° (Found: C, 68·2; H, 4·8; N, 6·2. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8; N, 6·1%).

(*b*) Phenyl 4-nitrosalicylate (20 g.) and ammonium chloride (10 g.) in 50% aqueous alcohol (1 l.) were refluxed with zinc dust (200 g.) for 4 hours. After removal of the zinc, the filtrate was concentrated under reduced pressure to *ca.* 350 ml. and cooled. The solid was collected and recrystallised from alcohol, giving needles of phenyl 4-aminosalicylate (16 g.), m. p. 145—146° undepressed on admixture with a specimen prepared by method (*a*) above.

Similarly prepared were o-, colourless plates (from alcohol), m. p. 86—88° (Found: C, 68·9; H, 5·15; N, 5·75. $C_{14}H_{13}O_3N$ requires C, 69·1; H, 5·35; N, 5·8%), m-, colourless needles (from 60% acetone), m. p. 129—130° (Found: C, 69·1; H, 5·2; N, 5·55%), and p-*tolyl* 4-*aminosalicylate*, colourless needles (from 50% alcohol), m. p. 112° (Found: C, 68·9; H, 5·6; N, 5·9%), β-*naphthyl*, colourless needles (from 80% alcohol), m. p. 160—161° (Found: C, 72·85; H, 4·5; N, 5·2. $C_{17}H_{13}O_3N$ requires C, 73·1; H, 4·65; N, 5·0%), m- (method *a* only), colourless needles (from 40% acetone), m. p. 157° (Found: C, 64·4; H, 5·0; N, 11·5. $C_{13}H_{12}O_3N$ requires C, 63·9; H, 4·9; N, 11·5%), and p-*aminophenyl* 4-*aminosalicylate*, colourless needles (from aqueous alcohol), m. p. 181° (Found: C, 63·7; H, 4·9; N, 10·9%).

Methyl 4-*Benzylsulphonamidosalicylate*.—Methyl 4-aminosalicylate (16·7 g.) in dry pyridine (150 ml.) was heated with toluene-ω-sulphonyl chloride (19·0 g.) at 100° for 30 minutes. The solution was poured into ice-water (1 l.) containing hydrochloric acid (200 ml.) and after 2 hours at 0° the solid product (27·3 g.) was collected, washed with cold water, and dried. *Methyl* 4-*benzylsulphonamidosalicylate* separated from methanol in colourless stout rods, m. p. 172—173° (Found: C, 56·4; H, 4·3; N, 4·6; S, 9·8. $C_{15}H_{15}O_5NS$ requires C, 56·1; H, 4·7; N, 4·4; S, 10·0%).

The ester (22·6 g.) was heated under reflux for 30 minutes with 4% sodium hydroxide solution (250 ml.), cooled, and acidified with dilute hydrochloric acid. 4-*Benzylsulphonamidosalicylic acid* separated from 50% ethanol in colourless needles (18·1 g.), m. p. 224° (decomp.) (Found: C, 54·3; H, 4·2; N, 4·6; S, 10·15. $C_{14}H_{13}O_5NS$ requires C, 54·7; H, 4·2; N, 4·55; S, 10·4%).

4-*Amino*-3 : 5-*di-iodosalicylic Acid*.—(*a*) Methyl 4-aminosalicylate (1 g.) in hot carbon tetrachloride (50 ml.) was treated with a solution of iodine chloride (2 g.) in carbon tetrachloride (10 ml.). The gummy solid which separated was triturated with 10% aqueous sodium hydrogen carbonate, to yield the crude ester (1·1 g.) as a pale brown solid. *Methyl* 4-*amino*-3 : 5-*di-iodosalicylate* separated from methanol in colourless feathery needles, m. p. 159° (Found: C, 23·5; H, 1·8; N, 3·3; I, 60·3. $C_8H_7O_3NI_2$ requires C, 22·9; H, 1·7; N, 3·3; I, 60·6%). Hydrolysis with boiling 10% sodium hydroxide (20 ml.) for 10 minutes afforded 4-*amino*-3 : 5-*di-iodosalicylic acid* as colourless needles, m. p. 180° (decomp.) (from aqueous ethanol) (Found: C, 21·3; H, 1·2; N, 3·5; I, 62·5. $C_7H_5O_3NI_2$ requires C, 20·7; H, 12·1; N, 3·5; I, 62·7%).

(*b*) To 4-aminosalicylic acid (36 g.) suspended in 95% alcohol (200 ml.) was added sulphuric acid (24 ml.), the temperature being kept below 50°. Iodine (59·2 g.) was added, and then hydrogen peroxide (36 ml. of 30%) dropwise with stirring during 30 minutes. The mixture was cooled and the product (89 g.) collected. Crystallisation from alcohol gave colourless needles, m. p. 180° (decomp.) undepressed on admixture with a specimen prepared by method (*a*) above.

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741. *An Explanation of the Preferential Formation of Certain Rings in Acetals of the Polyhydric Alcohols.*

By S. A. Barker, E. J. Bourne, and D. H. Whiffen.

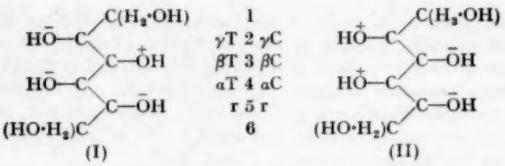
A detailed analysis is made of the stereochemical factors which govern the synthesis of cyclic acetals of the polyhydric alcohols; it relies on the basis that the most stable form of a polyhydric alcohol is that in which the carbon skeleton possesses a planar zig-zag structure. It is shown why certain types of cyclic acetals are possible while others are not, and why the different types are synthesised in the strict order of preference determined empirically by Barker and Bourne (*J.*, 1952, 905).

In a recent review of the condensation of polyhydric alcohols with acetaldehyde, benzaldehyde, and formaldehyde, Barker and Bourne (*J.*, **1952**, 905) presented empirical rules which enabled the structures of the products to be predicted; these rules, which were an extension of the Hann–Hudson rules (*J. Amer. Chem. Soc.*, **1944**, **66**, 1909; **1948**, **70**, 765), were: (1) the first preference is for a βC-ring; (2) the second for a β-ring; (3) the third for an α-, αT-, βT-, or γT-ring; (4) in methylenation, a βT-ring takes precedence over an αT- or a γT-ring; (5) in benzylidenation and ethylidenation, an αT-ring takes precedence over a βT- or a γT-ring; (6) rules (4) and (5) may not apply when one (or both) of the carbon atoms carrying the hydroxyl groups concerned is already part of a ring system. Such an order of preference—at first sight rather arbitrary—might be expected to have an underlying unifying principle, and the purpose of this paper is to show that the marked tendency for a carbon chain to adopt the planar zig-zag form (see McCoubrey and Ubbelohde, *Quart. Reviews*, **1951**, **5**, 364) is sufficient to explain the main features of the rules, since it appears that the most favoured rings involve the least energy for distortion of the planar chain. For brevity and clarity, all references to experimental data which were given by Barker and Bourne (*loc. cit.*) are omitted.

It will be recalled that the Greek letters, α, β, and γ, were used to signify the relative positions, along the carbon chain of the polyhydric alcohol, of the two hydroxyl groups engaged in the cyclisation, and that C and T indicated whether these two groups were disposed *cis* or *trans in the usual Fischer projection formula*; C and T were required only when *both* alcohol groups were secondary. Thus, a system in which an alkylidene residue spanned two secondary hydroxyl groups, located on adjacent carbon atoms and having a *trans*-orientation, was said to contain an αT-ring, whereas a β-ring was said to be present when one of the alcohol groups concerned was primary and the other was situated on the β-carbon atom. The same nomenclature is retained in the present paper, but is extended somewhat; in each case under discussion, the reference carbon atom is called C_r, and the others, C_α, C_β, etc., whilst the oxygen and hydrogen atoms are designated according to the carbon atoms to which they are united, *e.g.*, O_r and H_β are substituents on C_r and C_β, respectively. C_e refers to the external carbon atom belonging to the acetal addend.

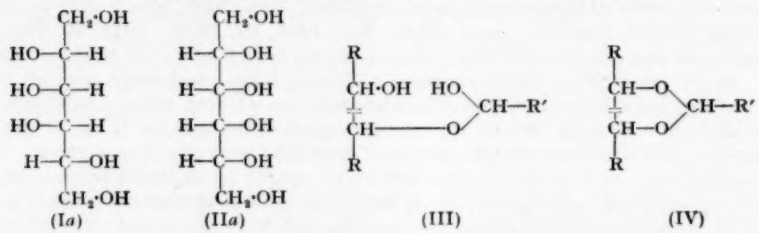
Before the relative merits of the various types of acetal rings can be assessed certain important factors must be considered, namely, the true spatial dispositions of the oxygen atoms in polyhydric alcohols (as distinct from the apparent dispositions seen in the usual Fischer projection formulæ), and the kinetics and energy changes involved in the formation of acetal rings. We take first the question of spatial dispositions. If it is accepted that the most stable arrangement in a polyhydric alcohol is that in which the carbon chain assumes a planar zig-zag form, then (I) and (II) represent the structures of talitol and allitol, respectively, viewed perpendicularly to the plane through the carbon atoms; for comparison, the Fischer projection formulæ for these hexitols are given in (I*a*) and (II*a*). It will be seen that, in (I) and (II), $O_{\alpha T}$, $O_{\beta C}$, and $O_{\gamma T}$ lie on the same side of the plane through the carbon atoms as does the reference oxygen atom, O_r, whilst $O_{\alpha C}$, $O_{\beta T}$, and $O_{\gamma C}$ lie on the opposite side. The distances between the various oxygen atoms shown in (I) and (II) are given in the Table; in calculating these distances, the bond angles at all carbon atoms were taken as the tetrahedral angle (109° 28′) and the bond lengths as C–C 1·54 and C–O 1·43 Å;

in subsequent calculations the length of the C–H bond will be taken as 1·09 Å. By using the same parameters, the O–O distance in an O–C_e–O group can be shown to be 2·34 Å, and so the oxygen atoms in a polyhydric alcohol which are already separated by a distance of this order are likely to participate most readily in acetal formation.



(I) (II)

$\overset{+}{O}$ represents an oxygen atom projecting towards the viewer.
$\bar{O}$ represents an oxygen atom projecting away from the viewer.
The hydrogen atoms at positions 2, 3, 4, and 5 are not shown.



(I*a*) (II*a*) (III) (IV)

When a polyhydric alcohol is treated with an aldehyde (R'·CHO) and a condensing agent there are many plausible condensations possible and the product would be a mixture containing acetal rings of different types, were it not for some controlling influence, which could be either the relative rates of the various reactions or the relative stabilities of the

Distances (Å) *from* O_r.

	O_α	O_β	O_γ	O_δ
C	3·68	2·51	5·11	5·02
T	2·83	3·43	4·54	5·54

products. The synthesis of a cyclic acetal (IV) is a two-stage process (cf. Meldrum and Vad, *J. Indian Chem. Soc.*, 1936, **13**, 118), involving first the formation of a semiacetal (III) and then cyclisation, with accompanying dehydration; the differences in the activation energies necessary for syntheses of acetal rings of different types will be essentially the differences in the amounts of energy required to form the transition states of virtually the same geometrical configurations as the final products. It is precisely this energy needed to distort the zig-zag carbon chain which controls the energy differences in the products, and hence their relative stabilities. It is for this reason that those acetal rings which are most readily synthesised are those which are most resistant to acidic hydrolysis (cf. Barker and Bourne, *loc. cit.*). Moreover, the fact that the above rules apply under a wide variety of reaction conditions supports the idea that the most stable acetals are formed most quickly. In the light of these general observations, it is possible to consider in detail the formation of individual types of rings, and thus to furnish an explanation of the rules. The assumption is made, probably quite legitimately, that the alkyl group and the hydrogen atom carried by the carbonyl group of an aldehyde do not prevent the distribution of the valency bonds of C_e from being tetrahedral, either in the semiacetal or in the cyclic acetal; *i.e.*, the O–O distance in the O–C_e–O group of these compounds will still be 2·34 Å.

Rule (1).—βC-*Rings*. It can be seen from the Table that the shortest O–O distance in the undistorted planar form of a polyhydric alcohol is 2·51 Å, the value for O_r–$O_{\beta C}$. Acetal formation, in which this distance is reduced to 2·34 Å, will require less distortion in this case than in any other. Indeed, a rotation of only 8° in the appropriate sense about each of

the bonds C_r–C_α and C_α–C_β will reduce the O_r–O_β distance to the required 2·34 Å without departure from tetrahedral angles at the carbon atoms.

Rule (2).—β-*Rings.* This rule deals with a terminal C_r, so that rotation about the C_r–C_α bond is possible without affecting the extended nature of the carbon chain. By such a rotation, O_r may be brought into the same position relative to O_β as is the normal one for $O_{\beta C}$, and acetal formation is possible with only the further, almost negligible, rotations of 8° mentioned under βC-rings. A β-ring is thus highly favoured, but further consideration of the rotation about C_r–C_α indicates why such a ring yields precedence to a βC-ring. It is unlikely that the most stable of the three configurations with a staggered arrangement about C_r–C_α (*i.e.*, with the deepest of the three potential minima) will be that corresponding to βC, since the O_r–O_β distance in this case would be 2·51 Å, which is less than the sum of the van der Waals radii for two oxygen atoms, namely 2·80 Å (see Pauling, "Nature of the Chemical Bond," Cornell Univ. Press, 1948, p. 189). The consequent repulsion energy is absent in the other positions, which therefore will be more stable. The fact that such repulsion energy must be overcome in passing from the most stable to the final position makes a β-ring less favoured than a βC-ring where the repulsion energy is present in the initial, as well as the final, state. Alternatively, even if all three potential minima be of essentially equal depth, only one-third of the molecules are in the βC-configuration and an entropy term, $\boldsymbol{RT}$ ln 3, has to be subtracted from the free energy of reaction, so that β-rings are again less favoured than βC-rings.

α-, αC-, and αT-*Rings in General.*—The minimum O_r–O_α distance encountered during a 360° rotation about C_r–C_α is 2·49 Å; it is reached when the two oxygen atoms are in the eclipsed position. Thus, an acetal requiring O_r–O_α 2·34 Å cannot be formed without distortion of either the bond lengths or the tetrahedral bond angles. If the bond lengths are unchanged and the angles O_r–C_r–C_α and C_r–C_α–O_α are reduced by 2·5° to 107°, the O_r–O_α distance is 2·37 Å in the eclipsed structure, which is exactly the required distance if the O_r–C_α–O_α angle is increased by 2·5° to 112°. The energy required for this small degree of distortion, 2·5° at each carbon atom concerned, is not very large, and depends partly on the nature of the addend.

Rule (3).—(a) α-*Rings.* Here the situation is very similar to that obtaining in the case of β-rings, because again C_r is terminal; the requisite state for acetal formation can arise by rotation about the C_r–C_α bond with very slight adjustment of bond angles (see above); the carbon skeleton of the polyhydric alcohol can still retain its extended form. However, an α-ring is formed less readily than βC- or β-rings, because, in the former case, the product possesses the unfavoured eclipsed structure for the valencies about the C_r–C_α bond, whereas, in the latter cases, it has essentially the favoured staggered structure about all the C–C bonds. All other known types of acetal rings in derivatives of polyhydric alcohols (namely, αT-, βT-, and γT-rings) can be formed only when the planar zig-zag carbon chain is seriously distorted, and consequently, in accordance with rule (3), they too are less probable than β-rings. There is no experimental evidence which would enable them to be compared with α-rings as regards ease of formation or stability.

(b) αT-*Rings.* After $O_{\beta C}$ the next nearest oxygen atom to O_r is $O_{\alpha T}$, situated 2·83 Å away in the extended chain form. Rotation by 60° about C_r–C_α is required to reach the eclipsed form; this implies definite distortion of the carbon chain, which remains essentially extended, but loses its planar character.

(c) βT-*Rings.* Reference to the Table shows that in the planar chain form of a polyhydric alcohol $O_{\beta T}$ lies 3·43 Å from O_r, a distance too great to permit cyclic acetal formation directly. This distance can be reduced to the required 2·34 Å by rotations about the C_r–C_α and C_α–C_β bonds; of the many ways in which this may be done, the simplest requires a rotation of 30° in the proper sense about each of these bonds. Again there is distortion of the planar chain and βT-rings, though possible, will not be highly favoured.

(d) γ*T-Rings.* A detailed analysis of the changes in the dispositions of the carbon atoms in a polyhydric alcohol which could result in a reduction of the O_r–$O\gamma_T$ distance from 4·54 Å (that in the zig-zag chain form) to 2·34 Å is complicated by the fact that rotations about the C_r–C_α, C_α–C_β, and C_β–C_γ bonds are all possible. Nevertheless, it is clear from models that the requisite transition state can arise, so that γT-rings are permissible. They are not

favoured, even compared to α-, αT-, or βT-rings, since the reaction state requires the co-operation of several rotations and the 2·34-Å distance will be reached only rarely; in other words the entropy decrease is large.

Rules (4) *and* (5).—These rules concern the order of precedence in the formation of αT-, βT-, and γT-rings. Although it is clear from the foregoing that βC-, β-, and probably α-, rings are preferred to αT-, βT-, and γT-rings because serious distortion of the extended carbon chain is necessary in the latter group, but not the former, it is much more difficult to differentiate between the energies involved in the formation of members of the latter group. Consequently there is a much finer balance in the order of preference within this group, a balance which can be upset by minor changes in the structure of the carbonyl component. Thus, a change in the nature of the addend from methylene to benzylidene or ethylidene may easily change the order of preference for αT- and βT-rings and necessitate the inclusion of the alternative rules (4) and (5).

Rule (6).—*The influence of pre-formed rings.* In this section consideration will be given only to the polyhydroxy-compounds reviewed by Barker and Bourne (*loc. cit.*); cyclitols will not be dealt with as they were discussed fully by Angyal and Macdonald (*J.*, 1952, 686) in a paper which appeared when the present contribution was in draft. The compounds containing pre-formed rings which are most frequently subjected to acetal formation are cyclic acetals themselves, formed in an earlier stage of the reaction, and these must be the first consideration. All cases in which the new acetal ring does not overlap the ring already present can be dismissed, because there is no new factor which would interfere with the usual order of preference; these cases include the introduction of the second β-ring in the dulcitol, mannitol, and perseitol series, and of an α-ring into the 1 : 3-2 : 4-diacetals of sorbitol and talitol. Nor is detailed analysis necessary of those cases in which the parent compound carries an acetal ring of the βC- or β-type, together with a suitable configuration of the remaining hydroxyl groups to permit the formation of a new βC- or β-ring (even when the new ring will overlap the old), because, as has been demonstrated already, βC- and β-rings are formed with negligible distortion of the extended chain; these cases include the formation of β-rings with 2 : 4-acetals of ribitol, xylitol, sorbitol, talitol, and their derivatives, and of βC-rings with 2 : 4-acetals of allitol and iditol.

In another convenient group of reactions, cyclic acetals which overlap pre-formed acetal rings are synthesised from derivatives of polyhydric alcohols carrying only two free hydroxyl groups; among these are those involving the introduction of (*a*) βT-rings into 2 : 4-acetals of 1 : 6-disubstituted derivatives of mannitol, (*b*) βT-rings into analogous compounds in the sorbitol series, (*c*) γT-rings into 1 : 3-4 : 6-diacetals of mannitol, (*d*) a γT-ring (methylene) into 1 : 6-dibenzoyl 3 : 4-benzylidene mannitol, and (*e*) an αT-ring (benzylidene) into 1 : 6-dibenzoyl 2 : 5-methylene mannitol. In (*a*) the rotation of 30° about $C_{(3)}$–$C_{(4)}$ to form the first βT-ring in the 2 : 4-position is in the same sense as that required for the second (3 : 5-)βT-ring, which should be formed therefore rather more easily than is usual. In (*b*), where the 2 : 4-ring is βC, the locked configuration about $C_{(3)}$–$C_{(4)}$ is not ideal for accommodating a βT-ring in the 3 : 5-position, yet it is still possible to form such a ring by rotation about the $C_{(4)}$–$C_{(5)}$ bond to bring O_3–O_5 to 2·34 Å, even though the arrangement is not that postulated as the "simplest" in the discussion of βT-rings. In (*c*), rotation about $C_{(3)}$–$C_{(4)}$ can lead to γT-ring formation, as discussed later in more detail. In (*d*) and (*e*) the product is the same, 1 : 6-dibenzoyl 3 : 4-benzylidene 2 : 5-methylene mannitol; the required rotation about the $C_{(3)}$–$C_{(4)}$ bond is in the same sense for the formation of the αT- and γT-rings, and in the parent compound for (*d*) the O_2–O_5 distance is already reduced from 4·54 to 3·01 Å, even before rotations occur about the $C_{(2)}$–$C_{(3)}$ and $C_{(4)}$–$C_{(5)}$ bonds. When the latter rotations also become effective—and there is no reason why they should not—this distance is reduced further, so that only small distortions of the bond angles are then needed to bring it to 2·34 Å; thus it can be seen why the αT- and γT-rings can exist together.

These arguments explain why it was possible to restrict the application of rule (6) to those acetal syntheses in which the parent compound was a derivative of a polyhydric alcohol carrying a cyclic substituent and free hydroxyl groups of such a configuration that a choice between αT-, βT-, and γT-rings was necessary, one or more of these hydroxyl

groups being attached to carbon atom(s) already forming part of the ring system. The only known reactions covered by rule (6) are (*a*) the methylenation of 1 : 3-methylene rhamnitol, and (*b*) the benzylidenation of 1 : 4-anhydrosorbitol and of its 6-chloro-6-deoxy- and 6-bromo-6-deoxy-derivatives. In (*a*) the usual order of preference for a βT-ring over a γT-ring is reversed, presumably because free rotation is no longer possible about $C_{(2)}$–$C_{(3}$ as is required for the " simplest " βT-case, so that the γT-ring is favoured relatively to the βT-ring; rotation remains possible about $C_{(3)}$–$C_{(4)}$, which is the most important requirement in the formation of a γT-ring. In (*b*), the reason why benzylidenation of 1 : 4-anhydrosorbitol leads to a βT-ring, rather than an αT-ring, is that $C_{(2)}$ and $C_{(3)}$ are part of the anhydro-ring system so that O_r and $O_{\alpha T}$ are fixed 3·68 Å apart, a limitation which does not apply to O_r and $O_{\beta T}$.

The Non-existence of Certain Types of Acetal.—αC-Rings. There seems to be no reason, on stereochemical grounds, why an αC-ring could not be formed from an acyclic polyhydric alcohol, just as it is in the cyclitol and sugar series. In the extended chain form of a polyhydric alcohol $O_{\alpha C}$ lies 3·68 Å from O_r; this distance can be reduced to that needed for acetal formation by a rotation of about 180° about C_r–C_α, followed by distortion of the angles by 2·5° as above, but this requires an eclipsed arrangement and also a considerable departure from the extended chain, making an αC-ring less probable than even an αT- or a βT-ring. It should be noted that when all the highly favoured βC- and β-configurations are satisfied in all unsubstituted tetritols, pentitols, and hexitols, and also in *gluco-gulo*-heptitol, and perseitol, then no αC-positions are available for acetal formation. There is no reported reaction in which an αC-ring fails to be formed after configurations suitable for all other rings have been satisfied.

γ-Rings. Since γT-rings have been proved experimentally to exist, the probable reason for a γ-ring not having been found is its lowly position in the order of preference; even if it were advanced in this order so that it followed βC- and β-rings, it could not possibly have been formed in any of the syntheses attempted to date, with the exception of the benzylidenation of arabitol and of the benzylidenation and methylenation of *gluco-gulo*-heptitol.

γC-Rings. Since these rings are bound to rank very low in the order of preference, lower even than γT- or γ-rings, there is little point in attempting to unravel the complexities of their possible synthesis from an unsubstituted polyhydric alcohol; instead, attention will be confined to the one known case in which there is a possibility of γC-ring formation without competition from other types of rings, namely, the attempted conversion of 1 : 3-4 : 6-diacetals of dulcitol into the corresponding 1 : 3-2 : 5-4 : 6-triacetals. The failure of this reaction is interesting in view of the successful introduction of γT-rings into the isomeric 1 : 3-4 : 6-diacetals of mannitol. The only C–C bond in the carbohydrate moiety of a 1 : 3-4 : 6-diacetal of either hexitol about which free rotation is still possible is the $C_{(3)}$–$C_{(4)}$ bond, and in each case there are two angles of twist which would bring the relevant oxygen distance to 2·34 Å, as required for the formation of the third ring; these angles are ±133° in the dulcitol series, and 149·5° and 86·5° in the mannitol series. However, in each of the dulcitol cases there is a non-bonded O–H distance (O_r–H_γ or O_γ–H_r) of 1·73 Å, which is so much smaller than the sum (2·60 Å) of the van der Waal's radii of hydrogen (1·20 Å) and oxygen (1·40 Å) (see Pauling, *op. cit.*) that the repulsive forces between these two non-bonded atoms would not be surmounted. There is no such objection to the 86·5° rotation in the mannitol series because this brings the O_r–H_γ and the O_γ–H_r distance to 3·57 Å, which presents no hindrance to the synthesis of a γT-ring. The 149·5° case gives both these O–H distances as 1·98 Å and must be ruled out.

Higher Rings.—Rings of the δ- or ε-types are inherently unlikely, and, in particular, no amount of rotation about the terminal C–C bonds of 2 : 4-3 : 5-diacetals of allitol or iditol will produce an O_r–O_ε distance suitable for ε-ring formation.

Formation of Cyclic Ketals.—Although the above arguments provide a satisfactory explanation of the rules concerning favoured ring forms in acetals of the polyhydric alcohols, it is still necessary to show why ketals are not formed in accordance with the rules, *i.e.*, why ketones often give rise to α- and αT-rings when β- and βC-configurations also are available [cf. Hermans (*Z. physikal. Chem.*, 1924, **113**, 337), who found that the condensation of acetone with propane-1 : 2-diol to give an α-ring was more complete than in the case of

β-ring formation from the isomeric 1 : 3-diol, the equilibrium constants being 0·44 and 0·026, respectively]. This discrepancy between aldehydes and ketones is probably due to a combination of factors, such as (*a*) the well-known reluctance of ketones to give semiketals with alcohols, and (*b*) the effect of two bulky alkyl groups on the O–C_e–O bond angle, and consequently on the O–O distance. It may well be, too, that ketones show a marked preference for addition to primary, rather than to secondary, hydroxyl groups of polyhydric alcohols and that, in the resulting semiketal, O_r and C_e will tend to continue the planar zig-zag carbon skeleton of the polyhydric alcohol. A partial explanation of the behaviour of ketones can be given on these lines, but it is not possible to make a detailed study until many more experimental data are available.

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742. *Synthesis of Fluoranthenes. Part XI.* Iodination of Tetrahydrofluoranthenes, leading to the Syntheses of 3-Methyl-1 : 2-5 : 6-dibenzopyracylene.*

By JOHN M. BEATON and S. HORWOOD TUCKER.

1 : 2 : 3 : 4-Tetrahydrofluoranthene and its 2- and 3-methyl derivatives (IV) have been directly iodinated to 5-iodo-derivatives (V). Dehydrogenation of these gave 4-iodo-, 5-iodo-2-methyl-, and 5-iodo-3-methyl-fluoranthene (VI), respectively. The last two, by the crossed Ullmann reaction, have been converted into 3-methyl-1 : 2-5 : 6-dibenzopyracylene (III).

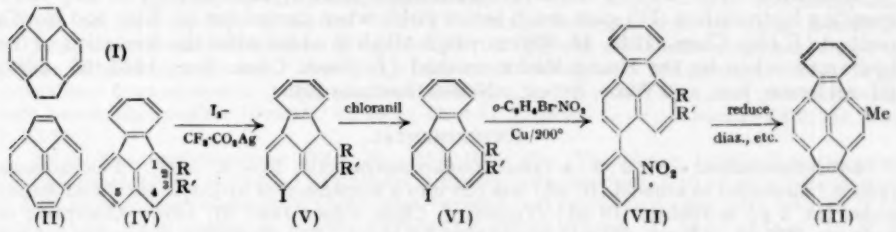
PYRACENE (I) has been synthesised by Anderson, jun., and Wade (*J. Amer. Chem. Soc.*, 1952, **74**, 2274) after many fruitless attempts (Mayer and Kaufmann, *Ber.*, 1920, **53**, 289; Fleischer and Wolff, *ibid.*, p. 925; Fieser and Peters, *J. Amer. Chem. Soc.*, 1932, **54**, 4347). Although pyracylene (II) has not been synthesised, four benzo-derivatives have been prepared : a monobenzo- (by Kloetzel and Chubb, *J. Amer. Chem. Soc.*, 1950, **72**, 150); a dibenzo- (by Stubbs and Tucker, *J.*, 1951, 2936); a tribenzo- (isorubicene) (by Fedorov, *Bull. Acad. sci., U.R.S.S., Classe sci. chim.*, 1947, 397; cf. Clar, *Ber.*, 1931, **64**, 2194, and Tucker and Whalley, *Chem. Reviews*, 1952, 529, footnote 2); and a tetrabenzo-pyracylene [by Badoche, *Ann. Chim.*, 1933, **20**, 200, and Dufraisse (Dufraisse and Girard, *Bull. Soc. chim.*, 1934, **1**, 1359; Dufraisse, *ibid.*, 1936, **3**, 1857; Dufraisse and Horclois, *ibid.*, p. 1894)].

Brown's molecular-orbital calculations (*J.*, 1951, 2391) for 1 : 2-5 : 6-dibenzopyracylene (Stubbs and Tucker, *loc. cit.*) give values which agree with those derived from its ultra-violet spectrum (Clar, Stubbs, and Tucker, *Nature*, 1950, **166**, 1075). To test Brown's predictions with regard to the position entered in electrophilic, nucleophilic, and radical substitution, reference compounds are being synthesised. At first, to test the generality of the method applied to the synthesis of the parent hydrocarbon, 1 : 2-5 : 6-dibenzopyracylene, we have similarly synthesised 3-methyl-1 : 2-5 : 6-dibenzopyracylene by two routes, and have widened the applicability of the method by starting with tetrahydrofluoranthenes instead of from fluoranthenes.

Although the direct action of electrophilic reagents on fluoranthene leads invariably, except under Friedel–Crafts conditions, to 4-monosubstituted derivatives, the yields are usually poor, since the mono- are separable with difficulty from poly-substituted derivatives (von Braun and Manz, *Annalen*, 1931, **488**, 111; cf. Garascia, Fries, and Ching, *J. Org. Chem.*, 1952, **17**, 227, who claim a "57% *crude*" yield of 4-nitrofluoranthene). Direct iodination by all the usual methods (including those described by Derbyshire and Waters,

* Part X, *J.*, 1952, 3187.

J., 1950, 3694; Barker and Waters, *J.*, 1952, 150; Henne and Zimmer, *J. Amer. Chem. Soc.*, 1951, **73**, 1362; Haszeldine and Sharpe, *J.*, 1952, 993) gave, at best, negligible quantities of 4-iodofluoranthene. It was, however, readily obtained as shown in the scheme. We find that fluoranthene can be conveniently hydrogenated to 1 : 2 : 3 : 4-tetrahydrofluor-



anthene by using Raney nickel at room temperature and under atmospheric pressure. Iodination of the tetrahydrofluoranthene was carried out with iodine and silver trifluoroacetate (Henne and Zimmer, *loc. cit.*). It is difficult to predict the position of substitution of 1 : 2 : 3 : 4-tetrahydrofluoranthene by this reagent; but it is found experimentally that electrophilic reagents invariably attack first the 5-position (von Braun and Manz, *Annalen*, 1932, **496**, 170). That this is also true of iodination by the above reagent, is now proved since dehydrogenation of the iodo-1 : 2 : 3 : 4-tetrahydrofluoranthene gives 4-iodofluoranthene, formerly prepared (Stubbs and Tucker, *loc. cit.*) from 4-nitrofluoranthene. The present work proves unmistakably that 1 : 2 : 3 : 4-tetrahydro-2- and -3-methylfluoranthene also iodinate similarly, to give 1 : 2 : 3 : 4-tetrahydro-5-iodo-2- and -3-methylfluoranthene, respectively.

It is also important to note that the iodinating reagent iodine trifluoroacetate (trifluoroacetyl hypoiodite) has been shown to be an ionic and not a radical reagent, *i.e.*, the reaction is an electrophilic attack by "positive" iodine (Henne and Zimmer, *loc. cit.*; Haszeldine and Sharpe, *loc. cit.*). Thus the possibility that in the iodination process iodine displaces hydrogen attached to a saturated carbon atom (as in $>CH_2$ or in $-CH_3$) is excluded.

2- and 3-Methylfluoranthene on hydrogenation appear to give tetrahydro-derivatives; but the products have not yet been utilised in these syntheses since we have not yet proved which ring is hydrogenated. Fortunately, 1 : 2 : 3 : 4-tetrahydro-2- and -3-methylfluoranthene (IV; R = Me, R′ = H; and R = H, R′ = Me, respectively) are readily obtainable (Tucker, *J.*, 1949, 2182; 1952, 807). Synthesis was accordingly conducted with both, as described below for the 2-isomer: 1 : 2 : 3 : 4-tetrahydro-2-methylfluoranthene (IV; R = Me, R′ = H) was iodinated (Henne and Zimmer, *loc. cit.*) giving 1 : 2 : 3 : 4-tetrahydro-5-iodo-2-methylfluoranthene (V; R = Me, R′ = H), which, on dehydrogenation with chloranil in xylene (Clar and John, *Ber.*, 1930, **63**, 2967), gave 5-iodo-2-methylfluoranthene (VI; R = Me, R′ = H). This, as in the analogous example of 4-iodofluoranthene (VI; R = R′ = H) (Stubbs and Tucker, *loc. cit.*), was subjected to a crossed Ullmann reaction with *o*-bromonitrobenzene, and gave 2-methyl-5-*o*-nitrophenylfluoranthene (VII; R = Me, R′ = H); this, *via* the corresponding amine, followed by diazotisation, gave 3-methyl-1 : 2-5 : 6-dibenzopyracylene (III). By the same sequence 1 : 2 : 3 : 4-tetrahydro-3-methylfluoranthene (IV; R = H, R′ = Me) (Tucker, *J.*, 1952, 803) was also converted into 3-methyl-1 : 2-5 : 6-dibenzopyracylene (III), thus providing conclusive proof of structure.

A crossed Ullmann reaction between 1 : 2 : 3 : 4-tetrahydro-5-iodofluoranthene (V; R = R′ = H) and *o*-bromonitrobenzene gave a poor yield of 1 : 2 : 3 : 4-tetrahydro-5-*o*-nitrophenylfluoranthene, discouraging the preparation of this type of compound as intermediate.

The close similarity of the ultra-violet absorption curves of 1 : 2-5 : 6-dibenzopyracylene (Clar, Stubbs, and Tucker, *loc. cit.*) and of the synthesised 3-methyl derivative supports the constitution assigned to the latter.

Synthesis of 1 : 2-5 : 6-dibenzopyracylene from methyl fluorene-9-carboxylate and the Mannich base, *o*-chlorophenyl 2-diethylaminoethyl ketone (Mannich and Dannehl, *Arch. Pharm.*, 1938, **276**, 206) as attempted with the corresponding nitro-compound (Stubbs and Tucker, *loc. cit.*) failed, since the initial condensation could not be effected.

Reduction of 1 : 2 : 3 : 4-tetrahydro-4-keto-2(or 3)-methylfluoranthene to the corresponding hydrocarbon (IV) gave much better yields when carried out by King and Nord's method (*J. Org. Chem.*, 1949, **14**, 638) in which alkali is added after the formation of the hydrazone—than by the Huang-Minlon method (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) (cf. Anderson, jun., and Wade, *loc. cit.*; Nelson, footnote 15).

Experimental

4-Iodofluoranthene.—1 : 2 : 3 : 4-*Tetrahydrofluoranthene* (IV; R = R′ = H). Fluoranthene (1·01 g.) suspended in ethanol (10 ml.) was run into a suspension of hydrogen-saturated Raney nickel (*ca.* 2 g.) in ethanol (10 ml.) (Tucker, *J. Chem. Educ.*, 1950, **27**, 489). Absorption of hydrogen (237 ml.; theory, 224 ml.) ceased after 2·5 hours. The crystalline suspension did not change in appearance. The mixture was boiled and filtered, the nickel extracted with boiling ethanol, the combined solutions evaporated, and the residue crystallised from methanol giving long rectangular blades of 1 : 2 : 3 : 4-tetrahydrofluoranthene (0·81 g., 80%), m. p. 72—75° (lit. 75°) (Found: C, 93·3; H, 6·6. Calc. for $C_{16}H_{14}$: C, 93·2; H, 6·8%). Hydrogenation proceeded slightly faster in ethyl acetate which had been kept for ½ hour over Raney nickel, then distilled from it. Reducing the relative amount of nickel slowed the reaction: thus, fluoranthene (10·1 g.), ethyl acetate (20 ml.), Raney nickel (3 g.), and ethanol (10 ml.) required 17 hours, but gave tetrahydrofluoranthene (8·84 g., 85%). There was no absorption of hydrogen when 5- or 10%-palladium–charcoal (Cheronis and Levin, *J. Chem. Educ.*, 1944, **21**, 603) was used in acetic acid solution (cf. von Braun and Manz, *Ber.*, 1930, **63**, 2608).

1 : 2 : 3 : 4-*Tetrahydro-5-iodofluoranthene* (V; R = R′ = H).—A mixture of 1 : 2 : 3 : 4-tetrahydrofluoranthene (4·12 g.), iodine (5·08 g.), carbon tetrachloride (40 ml.), and glass beads was treated with silver trifluoroacetate (4·42 g.) in portions with shaking and warming. Complete discharge of the iodine colour required addition of more silver salt (0·5 g.). The filtered residue was extracted (3 times) with carbon tetrachloride and the combined filtrates extracted with water (to recover trifluoroacetic acid). The evaporated organic layer gave a yellow residue which was dissolved in acetone, and the solution treated with excess of ethanol, to give colourless crystals, m. p. 119—123° (4·97 g., 75%). Purification was difficult, but finally from light petroleum (b. p. 60—80°) leaflets of 1 : 2 : 3 : 4-*tetrahydro-5-iodofluoranthene*, m. p. 121—125° (slight decomp.) were obtained (Found: C, 57·8; H, 3·9; I, 38·0. $C_{16}H_{13}I$ requires C, 57·85; H, 3·95; I, 38·2%). Attempts to iodinate tetrahydrofluoranthene with iodine in the presence of the usual oxidising agents, especially persulphuric acid (Elbs and Jaroslawzew, *J. pr. Chem.*, 1913, **88**, 92) gave high yields of fluoranthene, and often recovered tetrahydrofluoranthene, but no isolable iodo-compounds.

4-Iodofluoranthene (VI; R = R′ = H). 1 : 2 : 3 : 4-Tetrahydro-5-iodofluoranthene (0·38 g.) and chloranil (0·55 g.) in xylene (3 ml.) were boiled for 2 hours and then cooled. The crystals which separated were washed with benzene, and the benzene–xylene filtrate extracted with a 5% solution of sodium hydroxide containing sodium metabisulphite. Evaporation of the organic portion gave an oil which crystallised from light petroleum (b. p. 60—80°) in cream tufts (0·18 g., 47%). This was purified by crystallisation from ethanol and then formed cream leaflets, m. p. and mixed m. p. with 4-iodofluoranthene (Stubbs and Tucker, *J.*, 1951, 2936) 109—110°.

1 : 2 : 3 : 4-*Tetrahydro-5-o-nitrophenylfluoranthene.*—1 : 2 : 3 : 4-Tetrahydro-5-iodofluoranthene (1·33 g.), *o*-bromonitrobenzene (1·01 g.), and copper bronze (1 g.; added in portions) were heated at 200° for 6 hours. The melt was extracted with boiling benzene, and the filtered cold solution chromatographed (Al_2O_3). Unchanged *o*-bromonitrobenzene came through first, then a substance which crystallised from ethanol, and finally from ethyl acetate, in pale yellow leaflets (0·13 g., 10%) of 1 : 2 : 3 : 4-*tetrahydro-5-o-nitrophenylfluoranthene*, m. p. 152—154° (clear melt at 156°) (Found: C, 80·9; H, 5·0; N, 4·4. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·2; N, 4·3%).

3-*Methyl*-1 : 2-5 : 6-*dibenzopyracylene* (III).—*First synthesis—from* β-9-*fluorenylbutyric acid* (Tucker, *locc. cit.*). The acid was converted into 1 : 2 : 3 : 4-tetrahydro-4-keto-2-methylfluoranthene by the method given for the corresponding cyclisation of β-9-fluorenyl*iso*butyric acid (*J.*, 1952, 803). The ketone was crystallised from benzene–light petroleum (b. p. 60—80°):

the yield (62%) was as hitherto (*J.*, 1949, 2182). The ketone was reduced by King and Nord's method (*J. Org. Chem.*, 1949, **14**, 638; Tucker, *J.*, 1952, 803) in higher yield (75%) than that obtained (46%) when the Huang–Minlon process (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) was used (*J.*, 1949, 2182).

1 : 2 : 3 : 4-*Tetrahydro-5-iodo-2-methylfluoranthene* (V; R = Me, R′ = H). Iodination was carried out as described above for 1 : 2 : 3 : 4-tetrahydrofluoranthene by using 2-methyl-1 : 2 : 3 : 4-tetrahydrofluoranthene (1·1 g.), iodine (1·27 g.), and silver trifluoroacetate (1·1 g.) in carbon tetrachloride (10 ml.). More (0·3 g.) silver salt was added. The product (1·28 g., 74%) crystallised from ethanol in cream, nacreous leaflets, m. p. 131—132°, of 1 : 2 : 3 : 4-*tetrahydro-5-iodo-2-methylfluoranthene* (Found: C, 58·7; H, 4·5; I, 36·5. $C_{17}H_{15}I$ requires 59·0; H, 4·4; I, 36·7%).

5-*Iodo-2-methylfluoranthene* (VI; R = Me, R′ = H). The above tetrahydro-compound (1·0 g.) was dehydrogenated by 45 minutes' refluxing with chloranil (1·45 g.) in xylene (5 ml.). 5-*Iodo-2-methylfluoranthene* crystallised from benzene (red solution) flooded with ethanol (1 : 2 v/v) in pale green needles, m. p. 129—130° (0·71 g., 72%) (Found: C, 59·5; H, 3·2. $C_{17}H_{11}I$ requires C, 59·7; H, 3·2%). Chromatography had no further effect.

2-*Methyl-5-o-nitrophenylfluoranthene* (VII; R = Me, R′ = H). 5-Iodo-2-methylfluoranthene (0·47 g.) and *o*-bromonitrobenzene (0·30 g.) were heated at 195—200°, and copper bronze (0·3 g.; washed with carbon tetrachloride) added gradually with stirring during 2 hours. After further heating (2 hours) with occasional stirring, the melt was cooled, extracted with acetone, and filtered, the acetone removed, and the brown residue dissolved in benzene–light petroleum (b. p. 60—80°) (1 : 1) and chromatographed (Al_2O_3). The first pale yellow band to be eluted gave pale yellow needles, m. p. 117—119° (unidentified), from benzene–ethanol. The second bright yellow band, after concentration of its eluate and addition of ethanol gave bright, lemon-yellow, rectangular prisms of 2-*methyl-5-o-nitrophenylfluoranthene* (0·20 g., 42%), m. p. 172—174° (Found: C, 81·8; H, 4·6; N, 3·9. $C_{23}H_{15}O_2N$ requires C, 81·9; H, 4·5; N, 4·15%).

5-o-*Aminophenyl-2-methylfluoranthene*. The nitro-compound (0·09 g.), suspended in ethanol (5 ml.), was reduced by hydrogen in the presence of Raney nickel (0·4 g.); absorption ceased after 45 minutes. The heated mixture was filtered, the nickel residue extracted with hot ethanol, and the united filtrates evaporated, giving pale green, matted needles; recrystallisation (methanol) gave 5-o-*aminophenyl-2-methylfluoranthene*, m. p. 147—148° (0·06 g., 70%) (Found: C, 89·7; H, 5·3; N, 4·8. $C_{23}H_{17}N$ requires C, 89·9; H, 5·6; N, 4·6%).

3-*Methyl*-1 : 2-5 : 6-*dibenzopyracylene* (III). 5-o-Aminophenyl-2-methylfluoranthene (0·02 g.) was dissolved in acetic acid and poured with stirring into excess of 10% (v/v) sulphuric acid. A solution of sodium nitrite (0·01 g.) in water (1 ml.) was added to the slightly warm solution, which immediately became orange in colour. After the solution had been shaken (15 minutes) urea was added, and after a further shaking (15 minutes), copper bronze was added. After 15 minutes at room temperature and 15 minutes on the boiling-water bath the pale green solution was filtered and gave a residue which was extracted with benzene, and the dry orange solution chromatographed (Al_2O_3). The orange eluate, after concentration, gave orange needles which on crystallisation (acetone) gave 3-*methyl*-1 : 2-5 : 6-*dibenzopyracylene*, m. p. 205—206° (Found: C, 95·0; H, 4·9. $C_{23}H_{14}$ requires C, 95·1; H, 4·9%). It dissolves in cold concentrated sulphuric acid to a yellow solution, deepening to yellow-brown when heated. The *picrate*, brick-red micro-needles from benzene, has m. p. 193° (softening at 187°) (Found: C, 66·9; H, 3·1; N, 8·2. $C_{23}H_{14},C_6H_3O_7N_3$ requires C, 67·0; H, 3·3; N, 8·1%). The 2 : 4 : 7-*trinitrofluorenone* complex, scarlet needles from acetic acid containing a small amount of acetic anhydride, has m. p. 263—264° (Found: C, 71·4; H, 3·3; N, 6·9. $C_{23}H_{14},C_{13}H_5O_7N_3$ requires C, 71·4; H, 3·2; N, 6·9%).

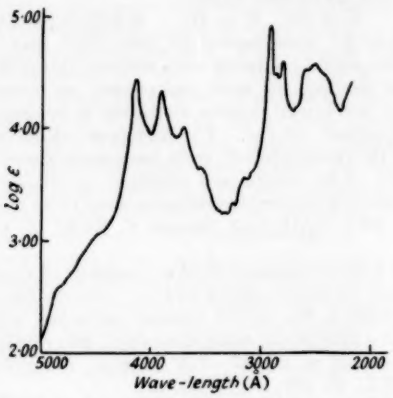
Renewed attempts to prepare the picrate of 1 : 2-5 : 6-dibenzopyracylene gave a mixture of bright yellow prisms, long scarlet needles, and stout orange-red polyhedra, from benzene. From dilute solutions it was possible to isolate the orange-red polyhedra, m. p. 200° (shrinkage at 180°), which were the *dipicrate* of 1 : 2-5 : 6-dibenzopyracylene (Found: C, 55·8; H, 2·6; N, 11·2. $C_{22}H_{12},2C_6H_3O_7N_3$ requires C, 55·6; H, 2·5; N, 11·4%). Recrystallisation of the polyhedra with slight excess of the hydrocarbon gave long scarlet needles mixed with yellow prisms. The 2 : 4 : 6-*trinitrofluorenone* complex of 1 : 2-5 : 6-dibenzopyracylene, brick-red micro-crystals from acetic acid–acetic anhydride, has m. p. 262° (Found: C, 71·3; H, 3·1; N, 7·2. $C_{22}H_{12},C_{13}H_5O_7N_3$ requires C, 71·1; H, 2·9; N, 7·1%). A mixture with the corresponding complex from 3-methyl-1 : 2-5 : 6-dibenzopyracylene had m. p. 255°.

Second synthesis—from β-9-*fluorenylisobutyric acid* (Tucker, *J.*, 1952, 803). The acid was

cyclised to 1 : 2 : 3 : 4-tetrahydro-4-keto-3-methylfluoranthene and this was reduced to 1 : 2 : 3 : 4-tetrahydro-3-methylfluoranthene, as recorded. Crystallisation of the last by addition of hot ethanol to a suspension in methanol until no oil separated on cooling gave practically colourless, rectangular plates, m. p. 47—49° (yield 77%).

All the 3-methyl derivatives described below were prepared by the methods used for the corresponding 2-methyl isomers (above).

1 : 2 : 3 : 4-*Tetrahydro-5-iodo-3-methylfluoranthene* (V; R = H, R′ = Me) was obtained in faintly green, short blades or needles (71%) (from ethanol), m. p. 110—111° (clear melt at 112°) (Found: C, 59·0; H, 4·6; I, 37·0. $C_{17}H_{15}I$ requires C, 59·0; H, 4·4; I, 36·7%). 5-*Iodo*-3-*methylfluoranthene* (VI; R = H, R′ = Me) crystallised from a concentrated solution in benzene to which a few drops of methanol were added, as salmon, diamond-shaped plates (78%), m. p. 113—114·5° (iodine-pink melt) (Found: C, 59·5; H, 3·35; I, 36·8. $C_{17}H_{11}I$ requires C, 59·7; H, 3·25; I, 37·1%). 3-*Methyl*-5-o-*nitrophenylfluoranthene* (VII; R = H, R′ = Me) was prepared at 200—210°. In the chromatographic separation, the first band gave pale yellow needles (ethanol), m. p. 100—102° (unidentified); the bright yellow second band, thick laths



3-*Methyl*-1 : 2-5 : 6-*dibenzopyracylene*.

prisms (55%), m. p. 138—140°, from ethyl acetate to which an equal volume of methanol was added (Found: C, 81·8; H, 4·4; N, 4·1. $C_{23}H_{15}O_2N$ requires C, 81·9; H, 4·5; N, 4·15%). 5-o-*Aminophenyl*-3-*methylfluoranthene* (VIII; R = H, R′ = Me) crystallised (ethanol) in green-yellow rhombohedral, thick plates (80%), m. p. 123—125°. When powdered, it exhibited in sunlight and in ultra-violet light a pale green fluorescence (Found: C, 90·1; H, 5·8; N, 4·7. $C_{23}H_{17}N$ requires C, 89·9; H, 5·6; N, 4·6%). On several occasions this compound separated in feathery crystals which on recrystallisation gave rhombs, as above, but softened at a lower temperature and were partly unmelted at 128°. The *acetyl* derivative, which formed pale green needles in burrs from petroleum (b. p. 80—100°) containing a trace of benzene, had m. p. 136° (softening at 133°) (Found: C, 85·9; H, 5·4. $C_{25}H_{19}ON$ requires C, 85·9; H, 5·5%).

3-Methyl-1 : 2-5 : 6-dibenzopyracylene (III), prepared from 5-*o*-aminophenyl-3-methylfluoranthene, had m. p. 205—206° alone or mixed with the material prepared from 5-*o*-aminophenyl-2-methylfluoranthene. The specimens prepared by the two routes were indistinguishable.

Ultra-violet Absorption Spectrum of 3-*Methyl*-1 : 2-5 : 6-*dibenzopyracylene*.—This was recorded on the Unicam spectrophotometer, ethanol being used as solvent: maxima occurred at (λ in Å) *p*-Bands: 4160 (log ε 4·46), 3930 (4·37), 3720 (4·06), 3560 (3·70). β-Bands: 2940 (4·99), 2880 (4·56), 2820 (4·68). β′-Bands: 2620 (4·60), 2540 (4·66).

We are grateful to Mr. A. J. N. Hope, B.Sc., for preparing the ultra-violet absorption curve; and to Mr. J. M. L. Cameron and Miss M. W. Christie for micro-analyses.

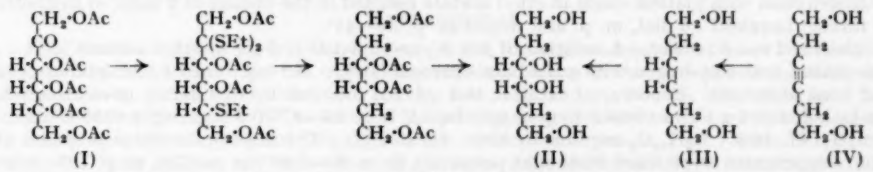
UNIVERSITY OF GLASGOW. [*Received, June 13th*, 1952.]

743. *Synthesis of Carbohydrates by Use of Acetylenic Precursors. Part III.** erythro-*Hexane*-1 : 3 : 4 : 6-*tetrol.*

By R. A. Raphael and C. M. Roxburgh.

erythro-Hexane-1 : 3 : 4 : 6-tetrol has been prepared by the *cis*-hydroxylation of *cis*-hex-3-ene-1 : 6-diol which was obtained by partial catalytic hydrogenation of the corresponding acetylenic compound. It was not identical with the substance to which this constitution has hitherto been ascribed.

In an attempt to prepare 2-deoxy-D-allitol Wolfrom, Lew, and Goepp (*J. Amer. Chem. Soc.*, 1946, **68**, 1446) treated keto-D-psicose penta-acetate (I) with ethanethiol and zinc chloride and subjected the resulting crude thioketal to Raney nickel hydrogenolysis. Very surprisingly the product, after deacetylation, proved to be a hexanetetrol and, since the compound proved to be devoid of optical activity throughout the visible spectrum, the American workers assigned to it the plausible *meso*-configuration *erythro*-hexane-1 : 3 : 4 : 6-tetrol (II). The mechanism proposed to account for the formation of (II) involved the replacement of the 5-acetoxy-group as follows :



In view of the unusual nature of this postulated reaction it was deemed desirable to devise an unequivocal synthesis of (II) for purposes of comparison.

The required starting material was the hitherto unknown hex-3-yne-1 : 6-diol (IV). Preparation from ethylene oxide and acetylenedimagnesium bromide was unsuccessful, the sole product being ethylene bromohydrin; this type of reaction between ethylene oxide and Grignard reagents has been noted before (see Gaylord and Becker, *Chem. Reviews*, 1951, **49**, 414). In the successful preparation the lithium compound of 4-(tetrahydro-2-pyranyloxy)but-1-yne was treated in liquid ammonia solution with ethylene oxide; acid hydrolysis of the resulting 6-(tetrahydro-2-pyranyloxy)hex-3-yn-1-ol produced the needed hex-3-yne-1 : 6-diol. Partial hydrogenation of this compound with palladised charcoal as catalyst yielded *cis*-hex-3-ene-1 : 6-diol (III); the corresponding *trans*-diol was obtained when sodium in liquid ammonia was used as the reducing agent. Treatment of the *cis*-diol with a *tert.*-butyl alcoholic solution of hydrogen peroxide containing osmium tetroxide resulted in *cis*-hydroxylation to furnish the required *erythro*-hexane-1 : 3 : 4 : 6-tetrol (II) as a crystalline solid (cf. Part I, *J.*, 1949, S45). The melting point of this tetrol (113—114°) and that of its dimethylene derivative (146—147°) showed it to differ from the compound obtained by the American workers (m. p. 121—122°; dimethylene derivative, m. p. 97—98°). The nature of the latter product is obscure.

Experimental

6-(*Tetrahydro-2-pyranyloxy*)*hex-3-yn-1-ol.*—To a stirred solution of lithamide (from lithium, 2·3 g., in the presence of ferric nitrate catalyst) in liquid ammonia (400 c.c.) was added dropwise (15 minutes) a solution of 4-(tetrahydro-2-pyranyloxy)but-1-yne (45·4 g.; Jones, Shen, and Whiting, *J.*, 1950, 235) in dry ether (25 c.c.), and stirring was continued for 40 minutes. Ethylene oxide (40 c.c.) was then added all at once and the reaction mixture stirred for 9 hours after which it was decomposed by addition of ammonia solution (*d* 0·88; 5 c.c.) and set aside overnight for the ammonia to evaporate. Ether and water were added, the aqueous layer was extracted with ether, and the ethereal solution was washed with brine, dried (Na_2SO_4), and

* Part II, *J.*, 1952, 401.

evaporated Distillation gave 6-(*tetrahydro-2-pyranyloxy*)*hex-3-yn-1-ol* (45 g., 77%) as a liquid, b. p. 116°/0·4 mm., n_D^{21} 1·4828, after a small fore-run (5·5 g.) of starting material (Found: C, 66·3; H, 9·3. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·15%). Catalytic hydrogenation of the compound in ethyl acetate in presence of platinic oxide resulted in the uptake of 2 mols. of hydrogen, to form 6-(tetrahydro-2-pyranyloxy)hexan-1-ol, b. p. 97°/0·5 mm., n_D^{21} 1·4570, the *phenylurethane* of which crystallised in plates, m. p. 73—74°, from light petroleum (b. p. 40—60°) (Found: N, 4·6. $C_{18}H_{27}O_4N$ requires N, 4·4%).

Hex-3-yne-1 : 6-diol.—6-(Tetrahydro-2-pyranyloxy)hex-3-yn-1-ol (5 g.) was added to a solution of concentrated sulphuric acid (4 c.c.) in methanol (90 c.c.) and set aside at room temperature for 48 hours. The mixture was then neutralised with methanolic sodium methoxide (phenolphthalein), the solution being kept cooled to room temperature. The methanol was then evaporated off under reduced pressure (an efficient splash-head was necessary) and the gelatinous solid residue extracted with hot ethyl acetate (3 × 50 c.c.). The filtered extract was taken to dryness and the residue dissolved in boiling benzene (50 c.c.). Filtration and cooling gave elongated plates (2 g., 70%) of *hex-3-yne-1 : 6-diol*, m. p. 77—79°; recrystallisation from benzene–light petroleum (b. p. 60—80°) gave the pure diol, m. p. 80—80·5° (Found: C, 63·25; H, 8·85. $C_6H_{10}O_2$ requires C, 63·15; H, 8·85%). Setting aside a concentrated solution of the diol and phenyl *iso*cyanate in dioxan at room temperature for several days gave the *bisphenylurethane* which crystallised from benzene, followed by ethanol, in plates, m. p. 173—174° (Found: C, 68·4; H, 5·6; N, 8·3. $C_{20}H_{20}O_4N_2$ requires C, 68·2; H, 5·7; N, 7·95%). Complete hydrogenation with platinic oxide in ethyl acetate resulted in the uptake of 2 mols. of hydrogen to furnish hexane-1 : 6-diol, m. p. and mixed m. p. 39—41°.

cis-*Hex-3-ene-1 : 6-diol*.—A solution of hex-3-yne-1 : 6-diol (1·5 g.) in ethyl acetate (60 c.c.) was shaken under hydrogen with palladium–charcoal (10%; 150 mg.) until 1 mol. of hydrogen had been absorbed. Removal of catalyst and solvent followed by distillation gave cis-*hex-3-ene-1 : 6-diol* (1·1 g.) as a viscous hygroscopic liquid, b. p. 86—87°/0·3 mm., n_D^{16} 1·4750 (Found: C, 61·1; H, 10·8. $C_6H_{12}O_2$ requires C, 62·0; H, 10·4%). The *bisphenylurethane* prepared at room temperature crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 107—108° (Found: C, 68·0; H, 6·2; N, 8·2. $C_{20}H_{22}O_4N_2$ requires C, 67·8; H, 6·3; N, 7·9%).

trans-*Hex-3-ene-1 : 6-diol*.—Hex-3-yne-1 : 6-diol (1 g.) was transferred from a dropping funnel to a stirred solution of sodium (1 g.) in liquid ammonia (50 c.c.) by dripping liquid ammonia through it. The cooled (alcohol–carbon dioxide) reaction mixture was stirred for a further 2 hours and then decomposed by addition of ammonium chloride (4 g.). After evaporation any residual ammonia was removed by warming under reduced pressure and the residue extracted with boiling ethyl acetate. Filtration, evaporation, and distillation gave trans-*hex-3-ene-1 : 6-diol* (0·8 g.) as a viscous, hygroscopic liquid, b. p. 88—90°/0·3 mm., n_D^{18} 1·4747 (Found: C, 60·7; H, 10·7%). The *bisphenylurethane* crystallised from toluene in plates, m. p. 161—162° (Found: C, 68·0; H, 6·1; N, 7·9%).

erythro-*Hexane-1 : 3 : 4 : 6-tetrol*.—A cooled (0°) mixture of *cis*-hex-3-ene-1 : 6-diol (0·8 g.) and hydrogen peroxide–*tert.*-butanol (2·7M; 3 c.c.) was treated with a solution of osmium tetroxide in *tert.*-butyl alcohol (2%; 0·1 c.c.) and set aside at 0° for 24 hours. Removal of solvent under diminished pressure gave a viscous syrup which crystallised after several days at 0°. Crystallisation from ethanol gave erythro-*hexane-1 : 3 : 4 : 6-tetrol* (0·2 g.) as prisms, m. p. 113—114° (Found: C, 48·0; H, 9·2. $C_6H_{14}O_4$ requires C, 48·0; H, 9·4%). Treatment of the tetrol with aqueous formaldehyde and hydrogen chloride by the method of Wolfrom, Lew, and Goepp (*loc. cit.*) gave a brown oil which was isolated by ether; evaporation gave an oil that rapidly solidified. Crystallisation from ethanol gave the *dimethylene* compound in plates, m. p. 146—147° (Found: C, 55·4; H, 7·8. $C_8H_{14}O_4$ requires C, 55·2; H, 8·1%). This derivative was obtained both from the pure crystalline tetrol and from the syrupy residue derived from the mother-liquors.

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744. *The Potentiometric Titration of Iodic Acid with Potassium Iodide in Sulphuric and Hydrochloric Acid Solutions.*

By H. T. S. Britton, R. E. Cockaday, and J. K. Foreman.

Iodic acid can be accurately titrated potentiometrically with potassium iodide in sulphuric acid or very dilute hydrochloric acid solutions, the reduction proceeding directly to iodine. In hydrochloric acid of higher concentrations (1—2N), two inflections in the titration curve show that iodic acid is first reduced quantitatively to iodine monochloride, and this, in turn, to iodine. In hydrochloric acid of still higher concentration (>5N), these two inflections appear before the correct amounts of titrant have been added, the amounts depending on the time taken for titration.

Müller and Junck (*Z. Elektrochem.*, 1925, **31**, 200) showed that potassium iodate can be titrated potentiometrically by potassium iodide in solutions containing hydrochloric acid, but they did not investigate solutions in which the concentration of acid exceeded 2N. In the present work a much wider range of concentrations has been studied, and it has also been shown that accurate titrations can be carried out in solutions containing sulphuric acid up to 6N.

Experimental

(i) *Titration in hydrochloric acid solution.* In Fig. 1 are given typical curves of the titration by N-potassium iodide of 100 c.c. of 0·005M-potassium iodate in the presence of the following concentrations: *A*, 0·1; *B*, 0·2; *C*, 0·25; *D*, 0·35; *E*, 1·0; *F*, 2·0; *G*, 5·0; *H*, 7·5N. The titrations were carried out at 19°, separate E.M.F.s being measured between the saturated Calomel Electrode and two independent bright platinum electrodes (1 cm. × 1 cm.) immersed in the solution. Both of these electrodes reached the same potential within 2—3 minutes, provided that the solution was thoroughly stirred after each addition of potassium iodide solution.

In titration *A* the solution became red on the addition of the first drops of potassium iodide solution and remained red even when stirred, but in titrations *B*—*H*, although a red colour was similarly produced at first, this became pale yellow when the solutions were stirred thoroughly. The pale yellow colour changed abruptly to red again at the points indicated by the first inflections. In all titrations, except *G* and *H*, iodine was ultimately precipitated.

(ii) *Titration in sulphuric acid solution.* Fig. 2 refers to similar titrations in sulphuric acid of concentrations 0·7, 1·7, 3·3, and 6·0N (curves *A*, *B*, *C*, *D*, respectively). The low potentials set up at the beginning of the titrations must have been caused by the lack of adequate "poise" in the iodate solutions. The solutions were red, and some iodine was precipitated as the titrations proceeded. At all four concentrations of sulphuric acid, the end-point inflections occurred with the addition of exactly 5 mols. of iodide as required by $KIO_3 + 5KI + 3H_2SO_4 \longrightarrow 3K_2SO_4 + 3H_2O + 3I_2$, and, unlike the titrations in hydrochloric acid solutions, the final inflections become more satisfactory the greater the concentration of sulphuric acid.

Discussion

Titration with hydrochloric acid. The indefinite inflections produced in the early part of curves *C* and *D* are attributed to the slowness of the first stage of the reduction in 0·25—0·35N-hydrochloric acid. The broken lines illustrate the effect of allowing longer times (5 minutes of vigorous stirring) after each addition of titrant before measuring the E.M.F.s. The titration curves so obtained ultimately became coincident with the original curves.

The first inflection of curves *E* and *F* and that of the broken curve *D* occur with 2 mols. of potassium iodide and thus correspond with the completion of the first stage of the reduction:

$$2KI + KIO_3 + 6HCl \longrightarrow 3ICl + 3KCl + 3H_2O \quad . \quad . \quad . \quad . \quad (1)$$

whence it appears that the pale yellow colour was that of iodine monochloride. The inflection of the broken curve *C*, with 1 mol. of potassium iodide, is ascribed to insufficient time having been allowed.

The E_h at the mid-point of the first section of curve *E* (*i.e.*, with 1 mol. of potassium iodide) is 1·10 volt, which is also the normal redox potential of $IO_3' + 6H^* + Cl' \longrightarrow$

$ICl + 3H_2O + 4F$. The higher potentials set up in the first section of curve *F* show the effect of the greater hydrogen-ion activity.

Curves *G* and *H* show that the first stage of the reduction was completed in 5N- and 7·5N-hydrochloric acid when 1·5 mol. of potassium iodide had been added. If in these concentrated acid solutions reduction is strictly stepwise, the first product would be either

FIG. 1.

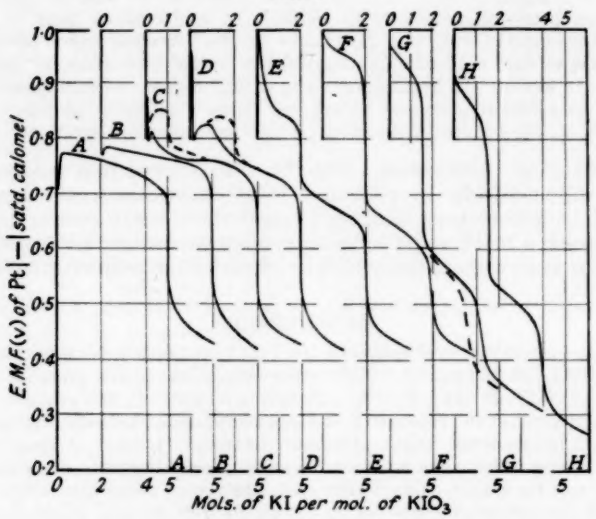
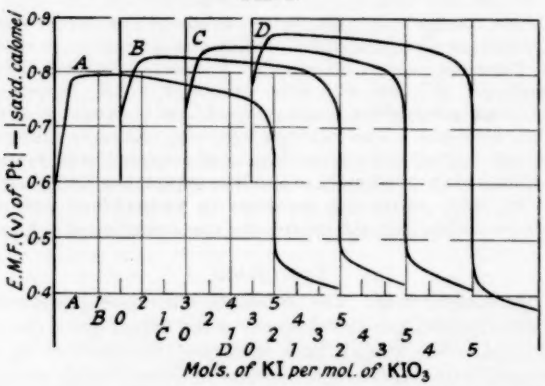


FIG. 2.



iodous acid, HIO_2, or the equivalent iodide trichloride, which would require 0·5 mol. of potassium iodide, and subsequent reduction of either of these to iodine monochloride would require a further 1·5 mols. of potassium iodide. The appearance of inflections in *G* and *H* with 1·5 mols. of potassium iodide may be connected with the formation of some iodine trichloride. Owing to the proximity of the redox potentials of the systems involving iodine trichloride and iodine monochloride no inflection would occur marking the formation of the former.

The final inflections of curves *A*—*F*, occurring with the addition of exactly 5 mols. of potassium iodide, correspond with the equation

$$KIO_3 + 5KI + 6HCl \longrightarrow 6KCl + 3I_2 + 3H_2O \quad . \quad . \quad . \quad . \quad (2)$$

but this can represent the mechanism of the reduction process only in titrations *A* and *B*. In the other titrations some iodine monochloride was produced, and curves *D*, *E*, and *F* reveal that, given sufficient time, 1 mol. of iodic acid is first quantitatively reduced according to equation (1), so that the subsequent reduction of the 3 mols. of iodine monochloride to iodine requires 3 mols. of potassium iodide :

$$3ICl + 3KI \longrightarrow 3KCl + 3I_2 \quad . \ . \ . \ . \ . \ . \ . \quad (3)$$

In titration *C*, therefore, a certain amount of iodic acid must have been directly reduced to iodine according to (2), the remainder undergoing stepwise reduction according to (1) and (3).

The appearance of the final inflections in curves *G* and *H* with 4·2 and 4·0 mols. of potassium iodide, respectively, must be attributed to the higher concentration of acid. Their precise location depends to some extent on the time taken over the titration as shown, *e.g.*, by the broken line at 3·8 mols. in *G*.

Consideration of Fig. 1 shows that for accurate results the concentration of hydrochloric acid should preferably be 0·1—0·35N (curves *A*—*D*) and should certainly not exceed 2N.

Two of the authors (R. E. C. and J. K. F.) thank the Ministry of Supply for granting facilities to carry out this work.

WASHINGTON SINGER LABORATORIES,
UNIVERSITY COLLEGE, EXETER.

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745. *An Electrometric Study of the Reaction between* (i) *Bromine and Iodide Ions in the Absence and in the Presence of Acid*; (ii) *Bromate and Bromide Ions in Acid Solution.*

By H. T. S. BRITTON and H. GREENSLADE BRITTON.

(1) Redox titrations of potassium iodide with bromine give inflections indicating the liberation of iodine and its conversion into iodine bromide. Bromine in acid solution, saturated with potassium bromide, may be titrated with potassium iodide to a good inflection corresponding to the formation of iodine bromide. When potassium bromide is absent, the bromine partially oxidises the iodide to iodate, the extent depending on the time allowed, and the iodide then reduces the iodate to iodine bromide and thence to iodine. Premature inflections denote the reduction to iodine bromide and iodine. When bromine-water is added to potassium iodide solution the oxidation to iodate involves the production of hydrobromic acid, the presence of which is shown by a rapid increase in conductivity and a decrease in pH.

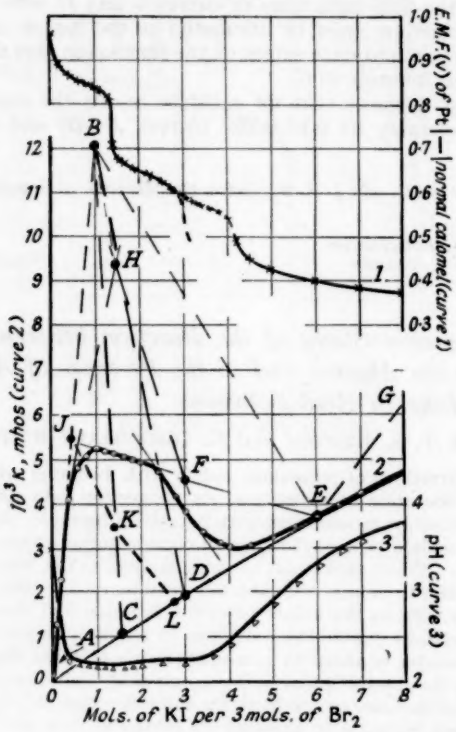
(ii) Potassium bromate in presence of sulphuric (but not hydrochloric) acid can be titrated with potassium bromide.

INSTEAD of the simple replacement reaction $Br_2 + 2KI \longrightarrow 2KBr + I_2$ when a solution of potassium iodide is gradually added to one of bromine or *vice versa*, a succession of reactions occurs. The reason for this is that bromine is a powerful oxidising agent, the standard redox potential of the bromine–bromide couple being 1·087 volt on the hydrogen scale, and that iodide ions are relatively powerful reducing agents, the standard redox potential of the iodide–iodine couple being 0·535 volt; hence, when iodide ions are slowly added to a solution of bromine they may first suffer oxidation to valency states higher than that of iodine, whereas in the reverse method of addition it would be expected that the iodide ions would be oxidised first to free iodine and ultimately to higher valency states. In the ordinary volumetric determination of bromine the oxidation of potassium iodide beyond the stage of free iodine is prevented by keeping the salt in large excess.

The objects of this work were (i) to study electrometrically the mechanism of the reactions taking place between bromine and iodide ions under various conditions, and (ii) to ascertain whether potentiometric titrations could be applied to the estimation of either

bromine or iodide ions. Some of the work was performed on bromine liberated by interaction of potassium bromate and potassium bromide in acid solution, and it was found that in the presence of sulphuric acid the quantitative reduction of bromate to bromine could be followed potentiometrically, the inflection indicating that only the reaction $KBrO_3 + 5KBr + 3H_2SO_4 \longrightarrow 3K_2SO_4 + 3Br_2 + 3H_2O$ had taken place. The potentiometric titration curves obtained when hydrochloric acid was present reveal that the reduction of the bromic acid passes through an intermediate stage and they fail to indicate its complete reduction to bromine. The positions of the two inflections in the

FIG. 1.



redox potentiometric curves obtained by titrating the bromine so liberated with potassium iodide depended largely on the concentration of potassium bromide in the original bromine solution: the greater this concentration the more rapid was the reaction.

EXPERIMENTAL

(1) *Reaction between Bromine-water and Potassium Iodide.*—The curves in Fig. 1 refer to the gradual addition of N-potassium iodide to 100 c.c. of 0·030N-bromine-water at 20°. In the bromine-water were two bright platinum electrodes (1 cm. × 1 cm.), and a saturated potassium chloride salt bridge connected the solution undergoing titration to the normal calomel electrode; the solution also carried a conductivity cell of the dip-type, the tube of a glass electrode, a stirrer, a tube for the introduction of nitrogen above the bromine-water, and a very fine tube for introduction of the potassium iodide solution from a microburette. As the vessel was fitted with an ebonite cap, loss of bromine or iodine through volatilisation was negligible.

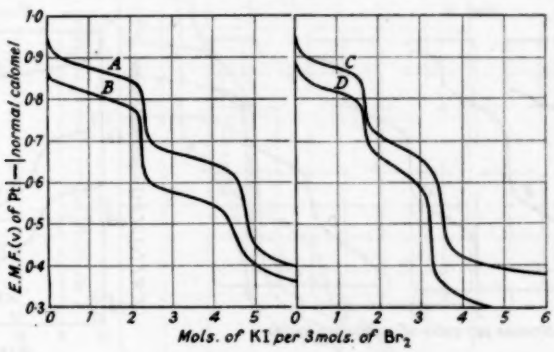
The reaction is illustrated by Fig. 1 in which curve 1 gives the change in redox potentials, curve 2 the specific conductivities, and curve 3 the pH values. The abscissæ represent mols. of potassium iodide per 3 mols. of bromine (2 horizontal divisions = 1 c.c. of N-potassium iodide).

The various measurements were sensibly steady for 5—10 minutes, except the redox potentials indicated by the broken line in curve 1, at which stage iodine was being precipitated and the potentials were drifting slowly to the higher values shown by the continuous curve. The broken line refers to the potentials that were set up after each fresh addition of titrant.

In curve 1 the first inflection appears with 1·35 mols. of potassium iodide and up to this point the colour of the solution was that of bromine, but here it suddenly changed to the orange colour of iodine and increased in intensity until iodine began to be precipitated. The final inflection occurred with 4·2 mols. of iodide and not with the stoicheiometrical amount, 6 mols. Curve 2 shows a remarkable initial increase in specific conductivity as the first 0·4 mol. of iodide was added, and since the pH correspondingly fell from 3·49 to 2·2 (curve 3), a strong acid was being produced. Curve 3 also shows that this acidity persisted until 4 mols. of iodide had been added, and then gradually decreased.

The curve *ACDE* gives the specific conductivities observed when 1·0N-potassium bromide was added to 100 c.c. of water at 20°, and these would have been the values observed during the addition of 6 mols. of iodide to 3 mols. of bromine had the reaction been simply $Br_2 + 2KI \longrightarrow 2KBr + I_2$, the contribution by the iodine being negligible. Thereafter, continued addition of potassium iodide would have caused curve 2 to follow the line *EG*; the complicated nature of the reactions concerned is demonstrated by the fact that the observed titration graph bears no resemblance to *AEG*.

FIG. 2.



(2) *Action of Potassium Iodide on Bromine in Aqueous Acids.*—The redox titration curves in Fig. 2 bring out clearly the important effect which acid has on the reaction between bromine and iodide ions. They refer to the titrations by N-potassium iodide of 100 c.c. of bromine solution containing either hydrochloric or sulphuric acid at the concentrations given in Table 1, which

TABLE 1.

Curve	Acid	Concn., N	KI, mols. 1st Inflin.	KI, mols. 2nd Inflin.	*f* *	Curve	Acid	Concn., N	KI, mols. 1st Inflin.	KI, mols. 2nd Inflin.	*f* *
A	HCl	0·2	2·35	4·70	0·78	*C*	H_2SO_4	0·7	1·68	3·50	0·56
B	HCl	2·0	2·30	4·58	0·77	*D*	H_2SO_4	7·0	1·73	3·34	0·58

* See p. 3886.

also records the number of mols. of iodide (per 3 mols. of bromine) required to produce the first and the second inflection of each curve. The E.M.F.s after each addition of iodide were measured as before; identical E.M.F.s were rapidly set up at the two electrodes after each addition of titrant and were stable for at least 5 minutes.

The sequence of visible changes was as described in (1). The amounts of potassium iodide needed to produce the second inflections of curves *A* and *B* were double those required to give the respective first inflections, but in titrations *C* and *D* this is only approximately true.

(3) *Addition of Bromine-water to Aqueous Solutions of Potassium Iodide.*—Fig. 3 gives the redox curves of titrations with 0·1168N-bromine-water of 100 c.c. of: (*A*) 0·025M-KI, (*B*) 0·025M-KI + 0·7N-H_2SO_4, (*C*) 0·025M-KI + 0·2N-HCl, and (*D*) 0·025M-KI + 2N-HCl. The observed E.M.F.s set up at the platinum electrodes when referred to the normal calomel

electrode are plotted against the equivalents of bromine added per equivalent of potassium iodide. In titrations *A*, *B*, and *C*, iodine was precipitated when rather more than ½ equiv. of bromine had been added, but it redissolved when just under 2 equivs. had been added; no precipitation occurred in titration *D*.

The first section of each curve refers to the simple displacement reaction $2KI + Br_2 \longrightarrow 2KBr + I_2$, the end of which is indicated by a well-defined inflection. The second section, terminated by an inflection which in the absence of acid is only just perceptible, corresponds to the oxidation of the iodine to iodine bromide in *A* and *B*, $I_2 + Br_2 \longrightarrow 2IBr$, and probably to iodine chloride in *C* and *D*: $I_2 + 2HCl + Br_2 \longrightarrow 2ICl + 2HBr$.

The bromine solutions used in the foregoing titrations were prepared directly from bromine and estimated volumetrically by normal procedure. As it was considered desirable that acidified bromine solutions of known concentration should also be prepared by some other method, we investigated the reaction between potassium bromate and potassium bromide in acid solution.

4. *Potentiometric Investigation of the Action of Potassium Bromide on Potassium Bromate in Acid Solution.*—Curve *A* in Fig. 4 is the redox titration curve of 100 c.c. of 0·005M-potassium bromate in 4N-sulphuric acid with 0·1M-potassium bromide and is typical of those in which the concentration of sulphuric acid lies between 3 and 6N. Bromine was liberated by the first drop of potassium bromide, and during most of the titration steady potentials were immediately set up, but towards the end they were obtained only after 5—10 minutes.

FIG. 3.

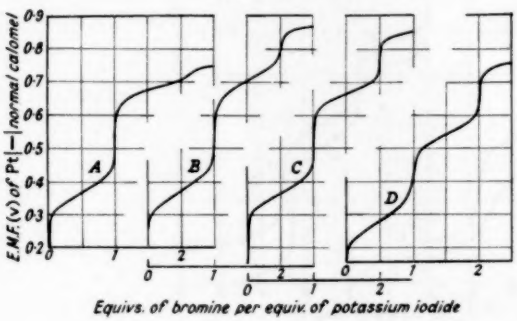
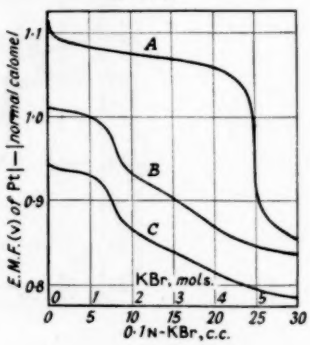


FIG. 4.



The position of the inflection in curve *A* corresponds exactly with the completion of the reaction given on p. 3880, the potentials before the inflection being those of the redox system $BrO_3' + 6H^{\cdot} \rightleftharpoons \frac{1}{2}Br_2 + 3H_2O + 5F$, and those after to $Br_2 \rightleftharpoons 2Br' + 2F$.

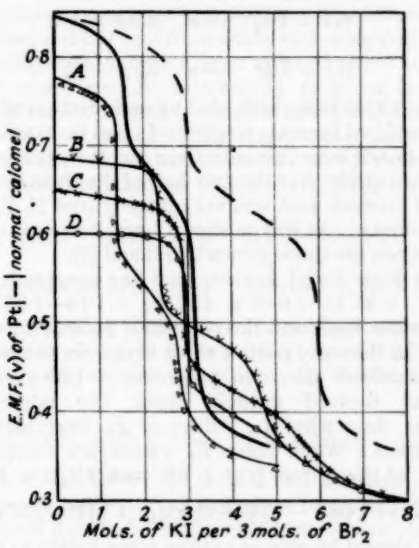
Curves *B* and *C* (Fig. 4) are those of similar titrations at 20° but in presence of 2N- and 5N-hydrochloric acid, respectively. Although bromine was liberated from the beginning of each of these two titrations, the fact that inflections occur with approximately 1·5 mols. of bromide per mol. of bromate indicates that some reaction must have occurred other than that which took place in titration *A*. Reduction to bromous acid would have required 0·5 mol. of potassium bromide, and to hypobromous acid, 2·0 mols. The inflection at an intermediate point may indicate simultaneous production of bromous acid and bromine, although the possibility of the formation of hypobromous acid cannot be excluded. That such titration curves should only be obtained with hydrochloric acid present suggests the production of bromine chloride in the course of the progressive reduction of bromic acid to bromine.

(5) *Effect of Bromide Ions on the Reduction of Bromine with Iodide Ions in Acid Solution.*—The " heavy " curve in Fig. 5 illustrates an immediate redox titration with N-potassium iodide of a solution prepared by adding 30 c.c. of 0·1M-potassium bromide to 100 c.c. of 0·005M-bromate + 4N-sulphuric acid, thereby yielding 130 c.c. of 0·0231N-bromine + 0·00385M-KBr + 3N-H_2SO_4. The two inflections occur at 1·58 and 2 × 1·58 (*i.e.*, 3·16) mols., respectively, of iodide per 3 mols. of bromine. As the stoicheiometric amount is 6 mols., it was suspected that one of the reactions involved in the reduction of bromine with bromide ions is slow and that in this titration insufficient time had been allowed for its completion. To ascertain whether this was the case, a number of solutions were taken, identical with that used before, but different quantities of N-potassium iodide were added. These solutions were kept in stoppered bottles,

with intermittent shaking, for 24 hours, and titrations were then continued with N-potassium iodide. In this time further reaction took place, so that the graph of total titration against potential was as shown by the broken line, the two inflections being at 3·0 and 6·0 mols. of iodide per 3 mols. of bromine.

Although the curves *B* and *C* in Fig. 4 do not reveal that in hydrochloric acid solution bromine is quantitatively liberated on addition of an excess of potassium bromide to potassium bromate, it is feasible to assume that this must ultimately be the case, and the following redox titrations were performed to ascertain the effect of (1) hydrochloric acid or (2) potassium bromide concentration on the manner in which bromine is reduced by iodide ions. In Fig. 5, curve *A* is that of the titration with 0·1N-potassium iodide of 150 c.c. of 0·00333M-potassium bromate containing hydrochloric acid (3·33N) and potassium bromide (0·033M). Curves *B*, *C*, and *D* refer to the titration by 0·1N-potassium iodide of 100 c.c. of 0·005M-potassium bromate, containing hydrochloric acid equivalent to 5N, which were (*B*) 0·192M; (*C*) 1·275M-, with respect to, and (*D*)

FIG. 5.



saturated with, potassium bromide. The curves refer to the immediate measurements of the E.M.F.s.

The depressing effect of the increasing concentrations of bromide ions on the potentials prevailing during the first and second sections of these titrations is apparent in Fig. 5. Referred to the arbitrary standard hydrogen electrode as of zero potential, the initial potentials indicated by curves *A*, *B*, *C*, and *D* are 1·058, 0·971, 0·940, and 0·883 V, respectively, and when these are compared with 1·085, the standard redox potential of the iodate–iodide couple, it appears unlikely that any appreciable concentration of iodide ions was oxidised initially to iodate ions in titrations *C* and *D*, although such oxidation is possible in *A* and perhaps to a small extent in *B*. Table 2 summarises the details of the concentrations of bromine and potassium bromide in the above solutions and of the inflections produced.

TABLE 2.

Curve	Bromine, N	KBr, N	KI, mols., at 1st Inflн.	KI, mols., at 2nd Inflн.	Curve	Bromine, N	KBr, N	KI, mols., at 1st Inflн.	KI, mols., at 2nd Inflн.
A	0·020	0·0167	1·40	2·82	*C*	0·030	1·25	2·90	5·80
B	0·030	0·167	2·40	4·80	*D*	0·030	Sat.	3·00	6·00

It is significant that the effect of increasing the concentration of potassium bromide is the elimination of the " slow " reaction, for the initial and final inflections are immediately produced

with 3 and 6 mols. of iodide (per 3 mols. of bromine). The curves in Fig. 5 also confirm the view that bromine is quantitatively liberated when an excess of potassium bromide reacts with potassium bromate in hydrochloric acid solution (see, however, curves *B* and *C* in Fig. 4).

Other redox titrations performed in solutions which contained either hydrochloric acid ranging from 0·2 to 5N or sulphuric acid ranging from 0·7 to 7N immediately produced curves that were inflected at 3 and 6-mols. of iodide provided that the solutions had been saturated with potassium bromide. Increase of acid concentration lowered the potentials set up at the platinum electrodes throughout the entire titrations by as much as 0·1 v, the extent depending on the concentration.

Discussion

Fig. 3 shows that, on addition of bromine to potassium iodide solution in equivalent amounts, iodine is liberated which, on addition of another equivalent, is immediately converted into iodine bromide. If therefore, these reactions take place in the reverse order when potassium iodide is added to a solution of bromine, the first reaction would be

$$KI + Br_2 \longrightarrow KBr + IBr \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and the second

$$KI + IBr \longrightarrow KBr + I_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

the completion of each reaction being indicated by an inflection when 3 mols. and 6 mols. of potassium iodide per 3 mols. of bromine respectively had been added. Although the redox curves in Figs. 1, 2, and 5 each have two inflections, yet it was only when (i) a very considerable time was taken, particularly over the first half of the titration (broken line, Fig. 5) and (ii) the concentration of bromide ions was very large (curve *D*, Fig. 5) that the inflections appeared with these amounts. As will be shown later, however, it is only under the latter conditions that the reactions are those shown by (1) and (2).

The redox curves in Figs. 1 and 2, show that the potentials at the beginning of the titrations varied from +0·85 to +0·97 v, *i.e.*, $E_h = 1{\cdot}13$—$1{\cdot}25$. The highest potential was set up in bromine-water itself and the potentials became smaller as the concentration of acid became larger. In the early part of these titrations the redox system was $Br_2 \rightleftharpoons 2Br'$, for which the standard electrode potential is 1·08 v, and since the bromide-ion concentration was derived entirely from the equilibrium $Br_2 + H_2O \rightleftharpoons H^{\cdot} + Br' + HBrO$, it is clear why the values of E_h were high and depended on the hydrogen-ion concentration. When these E_h values are compared with the standard redox potential, 1·085 v, of the system $IO_3' + 6H^{\cdot} \rightleftharpoons 3H_2O + I' + 6F$, for which

$$E_h = 1{\cdot}085 - (0{\cdot}058/6) \log_{10} [I']/[IO_3'][H^{\cdot}]^6$$

it appears that bromine should be able to oxidise some iodide to iodate ions, but owing to the lowering of E_h, which occurs as the oxidation proceeds through the change in the ratio [Red/[Ox], it is unlikely that the oxidation reaction

$$3Br_2 + 3H_2O + I' \rightleftharpoons 6H^{\cdot} + IO_3' + Br' \quad . \quad . \quad . \quad . \quad . \quad (3)$$

will proceed to completion, *i.e.*, with 1 mol. of iodide (to 3 mols. of bromine). None of the redox curves in Figs. 1, 2, and 5 is inflected at this point, however. If iodate ions were first formed, the absence of an inflection would indicate that the E_h range within which the next reduction process occurred could not have been very much lower than that previously set up by the bromine–bromide couple.

The conductometric curve (2) in Fig. 1 shows that the addition of the first 0·3 mol. of potassium iodide to bromine-water resulted in a sharp increase in conductivity, whereas the pH curve (3) reveals a corresponding fall in pH. Hence an appreciable concentration of a strong acid must have been produced. If iodide had been oxidised to iodate (3), then the increase in specific conductivity would have followed the line *AB*. That the increasing conductivity should have followed *AB* nearly to the point *J*, shows that a substantial fraction of 1 mol. of iodide ions had been so oxidised, but the less rapid increase in specific conductivity occurring during the addition of the remainder of the 1 mol. of potassium iodide suggests that some other reaction was then taking place.

If the reduction of iodate ions takes place in a stepwise manner on the progressive

addition of potassium iodide, then if iodous acid, HIO_2, or its derivative, IBr_3, is formed, the first step might be expected to follow either

$$KIO_3 + 1\tfrac{1}{2}HBr + \tfrac{1}{2}KI \longrightarrow 1\tfrac{1}{2}HIO_2 + 1\tfrac{1}{2}KBr \quad . \; . \; . \; . \; (4a)$$

or

$$KIO_3 + 6HBr + \tfrac{1}{2}KI \longrightarrow 1\tfrac{1}{2}IBr_3 + 1\tfrac{1}{2}KBr + 3H_2O \quad . \; . \; (4b)$$

Had the first mol. of iodide reacted entirely in accordance with (3), the change in specific conductivity would have been given by *AB*, and if this had been followed by reaction (*4a*) the subsequent change in conductivity would have been that indicated by *BC*, either reaction being complete when $1\frac{1}{2}$ mols. of iodide had been added. Had iodine tribromide been formed and it underwent no hydrolysis, the pH curve (3) would have been inflected with $1\frac{1}{2}$ mols. of iodide. It might be thought that as the redox curve (1) is inflected with 1·35 mols. of iodide, some iodous acid or iodine tribromide might have been formed, and that the slightly premature appearance of the inflection might have been caused by one or other of the reactions involved having been incomplete. The failure of the conductometric graph (2) to follow either course *ABH* or *ABC* renders such a supposition highly improbable. If iodous acid or iodine tribromide had then been reduced either to hypoiodous acid or to the corresponding iodine monobromide, another $1\frac{1}{2}$ mols. of iodide would have been required, making a total of 3 mols., and the respective section of the conductometric graph would have been *HF* or *CD*. It seems highly improbable, therefore, that reduction of iodate ions proceeds through the valency state of iodine of +3 to that of + 1.

It is much more likely that the reduction of iodate originally formed proceeded directly thus :

$$KIO_3 + 3HBr + 2HI \longrightarrow 3HIO + 3KBr \quad . \; . \; . \; . \; . \; (5a)$$

or

$$KIO_3 + 6HBr + 2KI \longrightarrow 3IBr + 3KBr + 3H_2O \quad . \; . \; . \; (5b)$$

If reduction had proceeded according to (*5a*) then the conductometric graph (2) would have been *ABF*, but if according to (*5b*) then it would have been *ABD*, and the pH curve (3) would have been inflected with 3 mols. of iodide. If, however, the iodate is reduced directly to iodine, thus

$$KIO_3 + 6HBr + 5KI \longrightarrow 3I_2 + 6KBr + 3H_2O \quad . \; . \; . \; . \; (6)$$

the conductometric graph would have been *ABEG* and inflection in the pH curve would have occurred with 6 mols. of iodide. Had reduction to either hypoiodous acid or iodine bromide taken place, the next 3 mols. of iodide would react in either of the following ways :

$$3HIO + 3HBr + 3KI \longrightarrow 3I_2 + 3KBr + 3H_2O \quad . \; . \; . \; (7a)$$

$$3IBr + 3KI \longrightarrow 3I_2 + 3KBr \quad . \; . \; . \; . \; . \; . \; . \; (7b)$$

so that the remaining part of the conductometric graph would have been either *FEG* or *DEG*, and if the former reaction had occurred an inflection in the pH curve would have appeared with 6 mols. of iodide.

Evidence has been advanced for the belief that hypoiodous acid or iodine bromide is formed in the course of the reduction of bromine with iodide ions. The potentials during the first section of curves *A*, *B*, *C*, and *D* in Fig. 5 show that in 5N-hydrochloric acid solution the increasing bromide-ion concentration depresses the redox potential. Associated with this lowering in E_h is the experimental fact that oxidation of the iodide ions proceeds rapidly to the valency state of +1, as shown by the inflection in *D* (Fig. 5) with 3 mols. of iodide. The depression of the initial redox potential to +0·60 v, *i.e.*, $E_h = +0{\cdot}88$ in this case below that of the iodate–iodide couple thereby renders impossible the oxidation of iodide to iodate ions. Hence in the absence of a large concentration of bromide ions the oxidation to iodate and/or the reduction of iodate to the +1 valency state are/is low. Owing to the close proximity of the standard redox potentials of the bromine–bromide and the iodate–iodide couples it is improbable that reaction (3) would proceed to completion. As shown in the preceding paper, the reduction of iodate with iodide in dilute acid solution

is not unduly slow, whence it would appear that the slow reaction is that represented by equation (3). It was also shown in the preceding paper that in the presence of sulphuric acid there is no evidence of the reduction of iodate ions to the intermediate +1 valency state of iodine. The curves in Figs. 2 (*C* and *D*) and 5 that refer to titrations in sulphuric acid solution are, however, inflected at points which correspond with the reduction to the +1 valency state, *i.e.*, to formation of either hypoiodous acid or iodine monobromide. In the case of the titrations depicted by Fig. 2 (*C* and *D*) the only hydrobromic acid available is that which was formed during the oxidation of iodide to iodate ions in an amount which was twice that required to convert the hypoiodous acid into iodine monobromide. For the reaction of potassium iodide with bromine-water the hydrobromic acid so produced is just sufficient, as shown by equations (3) and (5*b*), for the intermediate formation of iodine monobromide.

Hence, in the presence of a very large concentration of bromide ions, bromine is progressively reduced with iodide ions according to equations (1) and (2), but in the presence of a low concentration of bromide ions or in their absence some iodate is produced according to equation (3), and on addition of more potassium iodide the iodate is reduced by the successive reactions :

$$IO_3' + 3Hal' + 6H^{\cdot} + 2I' \longrightarrow 3H_2O + 3IHal \quad . \quad . \quad . \quad (5c)$$

$$3IHal + 3I' \longrightarrow 3I_2 + 3Hal \quad . \quad . \quad . \quad . \quad (2a)$$

In the last two equations Hal′ signifies either a Br′ or a Cl′ ion, for the latter ions are involved in hydrochloric acid solutions. There is little doubt that the first inflection of the redox titration occurs when the reactions (3) and (5*c*) have proceeded as far as possible in the available time. The second section terminating with the final inflection the reaction corresponds to equation (2*a*).

Attention has already been directed (p. 3881) to the fact that the amount of potassium iodide necessary to bring a redox curve to the first inflection was equal to that required further to produce the second inflection. An explanation is forthcoming if it be assumed that instead of 1 mol. of iodide ions reacting with 3 mols. of bromine according to equation (3), a fraction of 1 mol. of iodide ions, *f*, reacted in the time available to produce *f* mol. of iodate ions. Their reduction according to (5*c*) would require 2*f* mol. of iodide ions, thus making a total of 3*f* mol. of iodide ions to complete the first section of a redox curve. Equation (2*a*) would then demand another 3*f* mol. of iodide ions for the second section of the redox curve, *i.e.*, instead of 3 mols. of iodide ions being needed for each of the two sections of the reduction, 3*f* mols. would be used in each case. Hence in reaction of iodide ions with 3 mols. of bromine, 6*f* equiv. of iodine would at first be set free, the remainder, $6(1 - f)$, being very slowly liberated. In these considerations it has tacitly been assumed that the bromine which originally escaped reduction according to equation (3) did not begin to react with the iodide ions until reactions (5*c*) and (2*a*) had come to an end with the iodate ions first formed.

The column headed *f* in Table 1 gives the fraction of a mol. of iodide ions which had been oxidised to iodate in the different titrations. Table 1 shows that $f = 0{\cdot}77$—$0{\cdot}78$ for titrations carried out immediately in hydrochloric acid solution, whereas $f = 0{\cdot}56$—$0{\cdot}58$ for those in sulphuric acid solution. The broken-line curve in Fig. 5 shows that if adequate time be allowed *f* ultimately becomes unity.

By reasoning along these lines it is possible to give a more detailed explanation of the curves in Fig. 1. As the first inflection in the redox curve (1) occurs with 1·35 mols. of iodide, it follows that $f = 0{\cdot}45$, *i.e.*, 0·45 mol. of iodide reacts with bromine according to equation (3). In consequence, during the addition of this iodide the conductivity should increase along *AB* to the point *J*, and the pH should diminish correspondingly as shown by curves (2) and (3) in Fig. 1. If the remaining 0·90 mol. of iodide had reacted according to equation (5*a*), the conductivity would have fallen from *J* to *K*, whereas if the iodate had been converted into iodine bromide (equation 6*b*) the conductivity would have fallen from *J* to a point on *AC* immediately below *K*. If the subsequent reaction had been that indicated by equation (8*b*) the conductometric graph (2) would have followed the remaining

part of *AE*, the pH curve (3) would have been inflected upwards with 1·35 mols. of iodide, and the redox curve (1) would have been inflected a second time with 2·70 mols. of iodide (cf. broken line). Unlike those in titrations of bromine in acid solutions, the potentials during the second section were very unsteady and tended to higher values, with the result that the final inflection did not appear until after 4 mols. of iodide had been added; the conductometric graph showed larger conductivities than expected, and the pH curve showed that the solution remained appreciably acidic. These facts suggest that the potassium iodide was continuing to react with the unattacked bromine according to equation (3). It is probable that the iodate thus formed was subsequently reduced to iodine by the added potassium iodide and the free hydrobromic acid according to equation (6). Even so, just over two-thirds of the stoicheiometric amount of iodine was immediately liberated when 6 mols. of iodide (per 3 atoms of bromine) had been added. Because of the tardy manner in which iodine is liberated when potassium iodide is added to bromine, it is essential that in volumetric analytical procedure the reverse order be adopted, and to avoid the possible formation of iodine monobromide (cf. Fig. 3) the bromine to be estimated should be added to a much larger excess of potassium iodide in solution.

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746. *A Potentiometric Study of the Reduction by Potassium Iodide of Potassium Bromate in Sulphuric and Hydrochloric Acid Solutions.*

By H. T. S. BRITTON and H. GREENSLADE BRITTON.

Bromic acid can be accurately titrated potentiometrically with potassium iodide in sulphuric acid solutions over a wide range of concentration, but in hydrochloric acid solutions only when the acid concentration is not greater than 0·2N. In neither of these solutions is the mechanism of the reduction process given by the equation $BrO_3' + 6I' + 6H^+ \longrightarrow 3I_2 + 3H_2O + Br'$. Examination of the curves obtained leads to the two reaction sequences shown on p. 3892.

THIS work was undertaken to ascertain whether bromates in acid solution could be determined by potentiometric titration with potassium iodide. The first titrations, made on potassium bromate in dilute hydrochloric acid solution, revealed that, although apparently satisfactory redox titration curves could be obtained, their final inflections did not correspond with the theoretical equation $KBrO_3 + 6KI + 6HCl \longrightarrow 6KCl + 3I_2 + KBr + 3H_2O$, for not only were less than 6 mols. of potassium iodide needed, but the results were never reproducible. A systematic study was therefore made of the effects of the concentration of hydrochloric and sulphuric acid on the mode of the reduction of bromic acid with hydriodic acid in order (i) to find whether the potentiometric titration of bromates is possible and (ii) to gain some insight into the nature of individual reactions that occur.

It seemed probable that the premature variable inflections in the curves might have been caused by the slowness of the reaction between bromic and hydriodic acids (see, *inter alii*, Ostwald, *Z. physikal. Chem.*, 1888, **2**, 127; Meyerhoffer, *ibid.*, p. 585; Noyes, *ibid.*, 1895, **18**, 118; 1896, **19**, 599).

EXPERIMENTAL

Potentiometric Titration of Potassium Bromate by Potassium Iodide.—(1) *In sulphuric acid solution.* Fig. 1 gives typical curves showing the effect on the redox potentials, set up at bright platinum electrodes, of an increasing concentration of sulphuric acid. They refer to the titration at 20° of 100 c.c. of 0·005M-potassium bromate containing severally 2, 5, 10, and 20 c.c. of concentrated sulphuric acid (as indicated by numerals on the curve); for the first three

titrations, N-potassium iodide was the titrant, and for the last 0·1N-iodide. The abscissæ give the number of mols. of iodide added per mol. of bromate.

The first addition of iodide immediately gave the solution an orange tinge which on stirring changed to a pale yellow. This colour persisted until the first inflections were reached, after which one drop of the iodide caused the colour to change suddenly to that of iodine, which soon began to be precipitated. To ensure the reproducibility of the observed E.M.F.s (within 1 mv) two bright platinum electrodes (1 cm. × 1 cm.) were used and the solution undergoing titration was connected through a " salt bridge " of saturated potassium chloride solution to a normal calomel electrode.

The theoretical end-point, *i.e.*, 6 mols. of iodide per 1 mol. of bromate, is indicated in the first three titrations by well-defined inflections, but in the fourth curve the high concentration of sulphuric acid (*ca.* 8N) causes a premature inflection at 5·8 mols. of iodide. In each of the

FIG. 1.

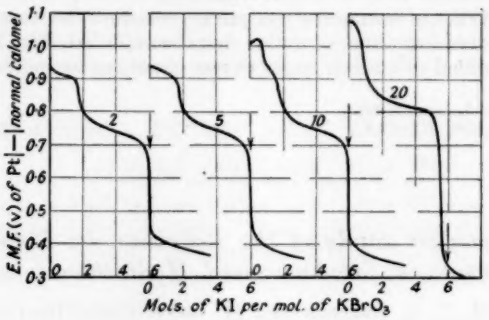
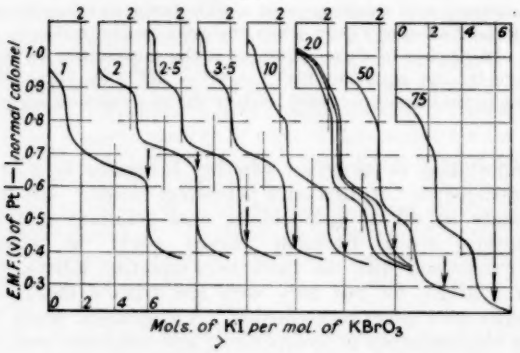


FIG. 2.



first three curves, inflections also appear with 1·67 mols. and in the last with 0·9 mol. In the third curve, too, a small inflection is discernible with 0·9 mol.

(2) *In hydrochloric acid solution.* In Fig. 2 are given similar curves for the titration by N-potassium iodide of a similar solution containing the volumes (c.c.) of concentrated hydrochloric acid denoted by the numerals. The three curves marked " 20 " show the effect of allowing greater time, after each addition of reductant, for the reaction to proceed before observing the E.M.F.s, those from left to right corresponding to readings after 1, 2, and 5 minutes' vigorous stirring after each addition. The other E.M.F.s were observed after 2 minutes' stirring after each addition, except that in the " 50 " curve potentials were recorded after 1 minute.

The colour changes resembled those in the presence of sulphuric acid, but it was only in the " 1 " and " 2 " titrations that iodine was precipitated. These two titrations were exceptional also in that the final inflections occurred when the stoicheiometric quantity of potassium iodide, 6 mols., had been added; in the more acid solutions they appeared prematurely, as shown in Table 1.

TABLE 1.

Curve	First section: Prel. inflin.	Final section: Mols. of KI at 1st Inflin.	2nd Inflin.†	*f* *	Curve	First section: Prel. inflin.	Final section: Mols. of KI at 1st Inflin.	2nd Inflin.†	*f* *
1	—	1·00	6·00	—	20 (i)	—	2·15	4·32 (4·30)	0·72
2	—	2·40	6·00	—	20 (ii)	—	2·45	4·90 (4·90)	0·82
2·5	0·22	2·10	5·60	—	20 (iii)	—	2·67	5·40 (5·34)	0·89
3·5	0·40	2·16	5·36	—	50	—	2·08	5·20 (4·16)	0·69
10	0·55	2·46	4·90 (4·92)	0·82	75	—	2·48	4·92 (4·96)	0·83

* See p. 3891. † The values in parentheses are double those at the first inflection.

(3) *Effect of Time on the Reactions occurring during Potentiometric Titration by Potassium Iodide of Potassium Bromate in Hydrochloric Acid Solution.*—The redox curves depicted in Fig. 3 show a reproduction of curve " 50 " from Fig. 2 (heavy line) together with curves corresponding to titrations of identical solutions to which had been added the amounts of potassium iodide shown in Table 2. Titrations were completed after the solutions had been

TABLE 2.

Curve	KI, c.c.	KI, mols.	Time (hr.)	KI, mols. 1st Inflin.	KI, mols. 2nd Inflin.	*f*	Curve	KI, c.c.	KI, mols.	Time (hr.)	KI, mols. 1st Inflin.	KI, mols. 2nd Inflin.	
" 50 "	0	0	0	2·08	4·20	0·69	*F*	1·50	3·00	24	3·00 (?)	5·96	1·00
A	0·50	1·00	26	2·64	5·28	0·88	*G*	1·80	3·60	44	—	5·94	—
B	0·80	1·60	27	2·84	5·66	0·95	*H*	2·00	4·00	28	—	5·96	—
C	1·00	2·00	24	2·86	5·74	0·95	*I*	2·25	4·50	40	—	5·92	—
D	1·10	2·20	4	2·76	5·56	0·92	*J*	3·00	6·00	48	—	—	—
E	1·45	2·90	5	2·90	5·80	0·97							

kept in stoppered bottles for the times stated, with intermittent shaking. In this way it was hoped to ascertain in which stage of the titration the slow reaction occurs. The solutions were pale yellow during the first section and red during the second.

DISCUSSION

Fig. 1 shows that, provided the concentration of sulphuric acid is not too high, it is possible to titrate potassium bromide with potassium iodide potentiometrically. Accurate results were obtained when the normality of the sulphuric acid was as high as 4, but in the presence of *ca.* 8N-acid the end-point inflection appeared prematurely, probably owing to some decomposition of the hydriodic acid by the sulphuric acid. In hydrochloric acid, however, as the first two curves in Fig. 2 show, it is only when its concentration is exceedingly low, *viz.*, 0·1—0·2N, that the final inflections appear at the theoretical point. With greater concentrations of hydrochloric acid the final inflections are produced with less than 6 mols. of potassium iodide, the amounts depending on the time taken to perform the titration, but as demonstrated by Fig. 3, the final inflection is very near the theoretical titre if a long time is allowed for completion of the reaction.

Earlier inflections occur in all the curves of Figs. 1 and 2 at points which correspond with an abrupt change in colour from a pale yellow to the orange-red imparted by free iodine. It is obvious that more than one reaction took place, so in those titrations in which accurate end-point inflections were obtained the theoretical equation can only be true in a composite sense in that it gives no information regarding the mechanism of the reduction.

It would be inferred from the standard redox potentials of the two systems :

$$BrO_3' + 6H^{\cdot} \longrightarrow 3H_2O + \tfrac{1}{2}Br_2 + 5F, \; \varepsilon_0 = 1{\cdot}52 \text{ volt}$$

and

$$BrO_3' + 6H^{\cdot} \longrightarrow 3H_2O + Br' + 6F, \; \varepsilon_0 = 1{\cdot}44 \text{ volt}$$

that the first stage in the reduction of the bromate ion would be to bromine itself, although the relative closeness of the two standard potentials might cause some reduction to bromide ions. Furthermore, the standard redox potential of the system $IO_3' + 6H^{\cdot} \longrightarrow 3H_2O + I' + 6F$ is 1·085 v, whence it appears that as a result of the oxidation of iodide to iodate by bromate, reduction of the bromate to bromine or bromide ions should be

possible. If in acid solution the bromate is reduced to (*a*) bromine, then the reaction would be

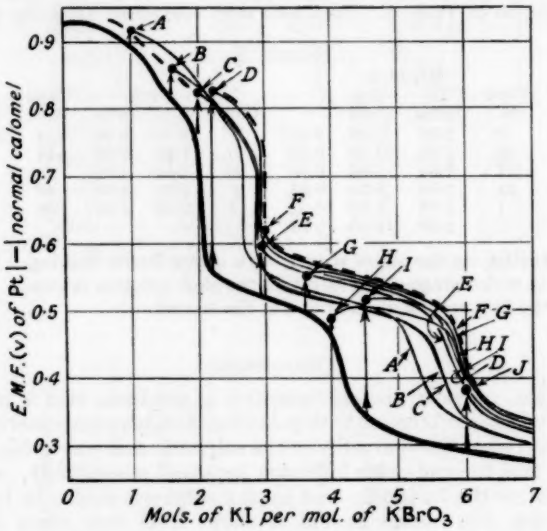
$$BrO_3' + H^{\cdot} + \tfrac{5}{6}I' \longrightarrow \tfrac{5}{6}IO_3' + \tfrac{1}{2}Br_2 + \tfrac{1}{2}H_2O \quad . \quad . \quad . \quad (1)$$

requiring $\frac{5}{6}$ mol. of iodide per mol. of bromate, whereas if to (*b*) bromide ions it would be

$$BrO_3' + I' \longrightarrow Br' + IO_3' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

requiring 1 mol. of iodide. In curve " 1 " in Fig. 2 the first inflection occurs with 1 mol. apparently indicating that reaction (2) must have been the first to take place. On the other hand, the preliminary inflection of curve " 10 " and the first inflection of curve " 20 " (Fig. 1) correspond with *ca.* 0·9 mol., which is of the order required by equation (1). The preliminary inflections of the " 2·5," " 3·5," and " 10 " curves in Fig. 2 are respectively

FIG. 3.



at 0·22, 0·40, and 0·55 mol. of iodide, probably owing to reactions (1) or (2) or both having taken place incompletely.

If the first reaction were that represented by equation (1), the bromine liberated would be expected to oxidise more iodide to iodate:

$$\tfrac{1}{2}Br_2 + \tfrac{1}{6}I' + \tfrac{1}{2}H_2O \longrightarrow Br' + \tfrac{1}{6}IO_3' + H^{\cdot} \quad . \quad . \quad . \quad . \quad (3)$$

If both reactions (1) and (2) occurred simultaneously, the redox system $Br_2 \rightleftharpoons 2Br'$ would be established, for which $\epsilon_0 = 1{\cdot}087$ v. Hence, whichever preliminary reactions may have taken place, the products of the reaction formed when 1 mol. of iodide has reacted completely should be in accord with equation (2).

The authors (preceding paper) have shown that reaction (3) is extremely slow, and should this reaction participate in the initial stage of the reduction of bromate ions with those of iodide it is highly probable that the reduction as a whole will be incomplete and the final inflections will appear before the stoicheiometric amount of potassium has been added (cf. curves " 2 " to " 75 " in Fig. 2).

It is significant in the " 2," " 5," and " 10 " curves in Fig. 1 that the first inflection should correspond with the addition of 1·67 mols. of iodide. If in each of these titrations, carried out in the presence of sulphuric acid, the slow reaction was eliminated and the first mol. of potassium iodide had reacted solely in accordance with equation (2) and the

iodic acid thereby formed had subsequently been reduced to iodine monobromide with more potassium iodide thus :

$$IO_3' + 6H^{\cdot} + 3Br' + 2I' \longrightarrow 3IBr + 3H_2O \quad . \quad . \quad . \quad . \quad (4)$$

then equation (2) reveals that only 1 mol. of the 3 mols. of bromide demanded by (4) existed in the solution. Hence only 1 mol. of iodine bromide could be formed, which involved $\frac{1}{3}$ mol. of iodate and $\frac{2}{3}$ mol. of iodide, and therefore for the completion of reaction (2) and the subsequent formation of 1 mol. of iodine bromide (4), a total of $1\frac{2}{3}$ mol. of iodide were required to bring each of the curves " 2," " 5," and " 10 " in Fig. 1 to their first inflection. Two reactions must consequently have occurred during the second sections of the " 2," " 5," and " 10 " sulphuric acid–bromate titrations, *viz.*, (4) and

$$\tfrac{2}{3}IO_3' + 4H^{\cdot} + \tfrac{10}{3}I' \longrightarrow 2I_2 + 2H_2O \quad . \quad . \quad . \quad . \quad . \quad (5)$$

thereby indicating the need of $4\frac{1}{3}$ mols. of iodide for the second section, making a total of 6 mols.

Table 1 and Fig. 2 show that in the presence of hydrochloric acid at concentrations equal to, or greater than, 0·2N, the first sections of the titration curves terminate at amounts of iodide which lie between 2 and 3 mols., whereas Table 2 and Fig. 3 reveal that when adequate time is allowed the first inflection is postponed until precisely 3 mols. of iodide have been added. The final inflection then appeared with 5·96 mols.

Another important observation is that the amounts of potassium iodide required to bring the curves " 10 " to " 75 " to their first inflection were one-half of that required to bring them to the respective final inflections (see Table 1). This relationship is again seen to exist in Table 2.

If it can be assumed that, had sufficient time been allowed after addition of 1 mol. of potassium iodide for the reaction, or reactions, shown by equation (2) to become complete, then the remaining reactions would be :

With 2 mols. of iodide (*i.e.*, a total of 3 mols.)

$$IO_3' + 2I' + 3Cl' + 6H^{\cdot} \longrightarrow 3ICl + 3H_2O \quad . \quad . \quad . \quad . \quad . \quad (6)$$

and with another 3 mols. of iodide (*i.e.*, a total of 6 mols.)

$$3ICl + 3I' \longrightarrow 3I_2 + 3Cl' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Thus there is reason to believe that reactions (6) and (7) take place spontaneously.

It has been suggested that the initial oxidation of iodide to iodate ions might take place according to either equations (1) or (2) or else first according to equation (1) and then, by the bromine thus set free, according to equation (3); in the latter case equation (2) becomes composite in that it incorporates both reactions by which 0·833 mol. of iodic acid would be produced according to equation (1) and the remaining 0·167 mol. by the slow reaction (3). The following is an attempt to explain why the two sections of almost every hydrochloric acid–bromate curve in Figs. 2 and 3 require equal amounts of potassium iodide. Owing to the slowness of one or both of the reactions included in the composite equation (2), we assume that in the time allowed a fraction, f, of a mol. of iodide is able so to react. Then in the presence of ample hydrochloric acid $2f$ mols. of iodide will be needed to reduce the f mol. of iodic acid to $3f$ mols. of iodine chloride (equation 6), which in turn will require another $3f$ mols. of iodide to liberate $3f$ mols. of iodine (equation 7). If it can be assumed that the oxidant, either bromine or perhaps potassium bromate, did not react with the potassium iodide until $6f$ mols. of iodide had been added, then $3f$ mols. of iodide would be required for the first section consisting of reactions (2) and (6) and another $3f$ mols. for the second section consisting of reaction (7) only. Hence,

$f = \frac{1}{3}$ (number of mols. of KI required by 1st section)

$= \frac{1}{6}$ (total number of mols. of KI indicated by final inflection)

Values of f so obtained are given in Tables 1 and 2. In Table 1, which refers to titrations carried out fairly rapidly, f varies from 0·69 to 0·89, although it is perhaps significant that of the six values recorded two should be 0·82 and one 0·83. Equation (1) requires $\frac{5}{6}$ mol.

(0·83) of iodide, whence it seems to follow that if the titration in hydrochloric acid is carried out moderately quickly the iodic acid produced results entirely from reaction (1). The allowance of too little time leads to values of f which are somewhat less than 0·83. Greater time enables f ultimately to become 1 as shown in Table 2.

Conclusion.—Our conclusions from the foregoing discussion are summarised herewith:

(i) In sulphuric acid solution the following reactions occur, the last two being simultaneous:

$$BrO_3' + I' \longrightarrow IO_3' + Br'$$
$$\tfrac{1}{3}IO_3' + Br' + 2H^{\cdot} + \tfrac{2}{3}I' \longrightarrow IBr + H_2O$$
$$\tfrac{2}{3}IO_3' + 4H^{\cdot} + \tfrac{10}{3}I' \longrightarrow 2I_2 + 2H_2O$$
$$IBr + I' \longrightarrow I_2 + Br'$$

(ii) In hydrochloric acid solutions of concentration >0·2N, instead of the first reaction above there occur:

$$BrO_3' + \tfrac{5}{6}I' + H^{\cdot} \longrightarrow \tfrac{5}{6}IO_3' + \tfrac{1}{2}Br_2 + \tfrac{1}{2}H_2O$$
$$\tfrac{1}{2}Br_2 + \tfrac{1}{6}I' + \tfrac{1}{2}H_2O \longrightarrow \tfrac{1}{6}IO_3' + HBr$$

of which the latter is very slow. If adequate time is allowed for completion of the reaction, then follow successively:

$$IO_3' + 2I' + 3Cl' + 6H^{\cdot} \longrightarrow 3ICl + 3H_2O$$
$$3ICl + 3I' \longrightarrow 3I_2 + 3Cl'$$

Otherwise, only the iodate ions initially formed will undergo reduction according to the last two equations, and any bromine which failed to react according to the second equation will thereafter slowly react with iodide ions.

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747. *A Potentiometric Study of the Reaction between Nitrous Acid and Hydriodic Acid.*

By H. T. S. BRITTON and H. GREENSLADE BRITTON.

Nitrous acid and hydriodic acid, liberated from their salts by hydrochloric acid, interact in two ways simultaneously:

$$2HNO_2 + 2HI \longrightarrow I_2 + 2NO + 2H_2O \quad . \quad . \quad . \quad (1)$$
$$2HNO_2 + 4HI \longrightarrow 2I_2 + N_2O + 3H_2O \quad . \quad . \quad . \quad (2)$$

If potassium iodide is added to nitrous acid in 10—15N-sulphuric acid, reaction (1) occurs, but in 2—7·5N-sulphuric acid both (1) and (2) occur. Similar addition in hydrochloric acid solution leads to (1) and (2) unless the concentration of hydrochloric acid is $\geqslant$5N, in which case two successive reactions occur:

$$HI + 2HNO_2 + HCl \longrightarrow ICl + 2H_2O + 2NO \quad . \quad . \quad (3)$$
$$HI + ICl \longrightarrow HCl + I_2 \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The dissociation constant of nitrous acid at 20° is 7×10^{-4}.

THE object of this work was to study the reaction between nitrous and hydriodic acids in solutions of hydrochloric acid and sulphuric acid at different concentrations. As the formation of nitrous acid from sodium nitrite by a strong acid was followed with the glass electrode, the dissociation constant of nitrous acid was calculated from the pH values observed as it was gradually released; as this constant had not hitherto been determined potentiometrically, the values obtained are recorded.

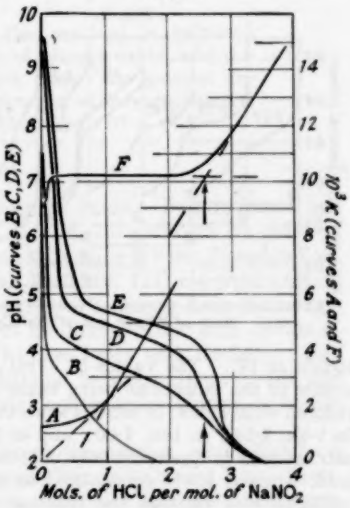
Experimental

Dissociation Constant of Nitrous Acid.—This was calculated from the pH values as determined with the glass electrode at 20° during the titration of (*a*) 100 c.c. of 0·0125M-sodium nitrite with 0·0883N-hydrochloric acid, (*b*) 50 c.c. of 0·05M-nitrite with 0·0883N-acid. In the table, (*a*) and (*b*), are recorded some of the observed pH values and the values of pK_a and K_a calculated

(*a*) HCl, c.c.	pH	pK_a	$K_a \times 10^4$	(*b*) HCl, c.c.	pH	pK_a	$K_a \times 10^4$
1·0	4·30	3·15	7·08	1·0	4·59	3·15	7·08
3·0	3·77	3·14	7·24	5·0	3·80	3·15	7·08
5·0	3·47	3·15	7·08	10·0	3·43	3·15	7·08
7·0	3·24	3·14	7·24	15·0	3·12	3·14	7·24
9·0	3·05	3·15	7·08	20·05	2·83	3·13	7·41
11·0	2·87	3·16	6·92	25·05	2·54	3·13	7·41
	Mean	3·15	$7·1 \times 10^{-4}$			3·14	$7·2 \times 10^{-4}$

therefrom. As the accuracy of the observed pH values is of the order of ±0·01 pH unit and as no correction has been made for the activity coefficients of the ions, the agreement between the two mean values of K_a, $7·1 \times 10^{-4}$ and $7·2 \times 10^{-4}$, is considered satisfactory. These values are slightly higher than those previously published, which were derived from measurements of electrical conductivity, kinetics, solubility of carbon dioxide in sodium nitrite solutions, and pH values estimated by means of indicators. The values so obtained vary from 4·0 to $6·2 \times 10^{-4}$ at 15—18° (Klemenc and Hayek, *Monatsh.*, 1929, **53**, 407; Arndt, *Z. physikal. Chem.*, 1903, **45**, 574; Ray, Dey, and Ghosh, *J.*, 1917, **111**, 416; Schmidt, *Z. Elektrochem.*, 1936, **42**, 582; *Angew. Chem.*, 1936, **49**, 378; Klemenc and Pollak, *Z. physikal. Chem.*, 1922, **101**, 157; Bauer, *ibid.*, 1906, **56**, 215; Dhar and Datta, *Z. Elektrochem.*, 1913, **19**, 407; Blanchard, *Z. physikal. Chem.*, 1902, **41**, 706).

Fig. 1.



Reaction between Nitrous and Hydriodic Acids.—(i) *In hydrochloric acid solution.* (*A*) Curve *B* in Fig. 1 gives the change in pH as nitrous acid is displaced from sodium nitrite by hydrochloric acid; it is a glass-electrode titration curve of 100 c.c. of 0·0125M-nitrite with 1·09N-acid. Curve *A* illustrates the change in specific conductivity during the same titration at 20°. Curves *C*, *D*, and *E* show the effect on the pH values of inserting increasing concentrations of potassium iodide in the sodium nitrite solutions when titrated with 1·09N-hydrochloric acid. These refer respectively to the titrations of 100 c.c. of 0·0125M-nitrate + *x*M-iodide, where $x = 0·075$, 0·75, and 1·50 for the respective curves. Curve *F* is the conductometric titration graph of the same solution as used for *C* with 1·09N-hydrochloric acid. The initial pH of solution *C* was 7·57, that of *D* 9·38, and that of *E* 9·44.

When solutions of the separate salts were mixed, a little iodine was liberated and made the solutions yellow. Hence some interaction must have occurred between the nitrite and iodide ions and so rendered the solutions alkaline. Curves *D* and *E* show that the solutions remained above pH 7 during the addition of 0·25 mol. of hydrochloric acid. Had no reaction occurred between the nitrite and iodide ions, the pH curves *C*, *D*, and *E*, would have been identical with curve *B*, as is the case when mixtures of sodium nitrite and potassium bromide, and of sodium nitrite and potassium chloride, are treated with hydrochloric acid. Moreover, the conductometric graph *F* would have been similar in form to *A*.

The inflections of curves *C*, *D*, and *E* show that 2·60, 2·61, and 2·75 mols. respectively of acid per mol. of sodium nitrite were required to bring the reactions between nitrite and iodide ions to completion, and these amounts are confirmed by the " breaks " in the corresponding conductometric graphs; *e.g.*, that of *F* confirms the location of the poorly-defined inflection in *C*. These curves show that in addition to the 1 mol. of hydrochloric acid needed to displace the nitrous acid from its salt, 1·60—1·75 mols. of acid were required to release equivalent amounts of hydriodic acid from the iodide which must have immediately reacted with the nitrous acid.

To account for such quantities it is evident that the interaction did not occur according to a single equation but to at least two equations, *viz.*, (1) and (2) (above) to different extents. The greater amount of hydrochloric acid required in titration *E* suggests that a relatively high concentration of iodide tends to favour reaction (2).

Whichever of these reactions occurs when an alkali nitrite is mixed with an alkali iodide in solution, hydrogen ions must be the essential reactants, for it is their removal from the water and reaction with nitrite and iodide ions, *e.g.*, $4H^{\cdot} + 2NO_2' + 2I' \longrightarrow I_2 + 2H_2O + 2NO$, that render the solution alkaline, as shown by the initially high pH values in titrations *E*, *D*, and *C*.

(*B*) The redox titration curves of 100 c.c. of 0·025M-sodium nitrite + *x*N-hydrochloric acid with 2N-potassium iodide at 18° are plotted in Fig. 2, the values of *x* being recorded on the respective curves, but the upper of the two curves marked 2·5 relates to 100 c.c. of 0·0375M-nitrite. When read from left to right, the inflections reveal that 1·25, 1·25, 1·25, 1·15, 1·00, and 1·00 mols. of hydriodic acid had reacted with one mol. of nitrous acid. Hence in 5·0—7·5N-hydrochloric acid solutions nitric oxide was the sole product of reduction of nitrous acid, whereas in 0·27—2·5N-solutions of the acid, a little nitrous oxide was also formed.

(ii) *In sulphuric acid solution.* Fig. 3 gives the redox titration curves, obtained with bright platinum electrodes, of 100 c.c. of 0·0125M-sodium nitrite + *x*N-sulphuric acid with N-potassium

FIG. 2.

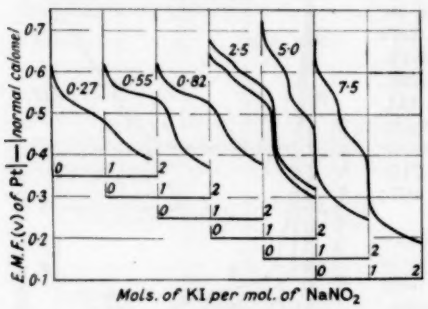
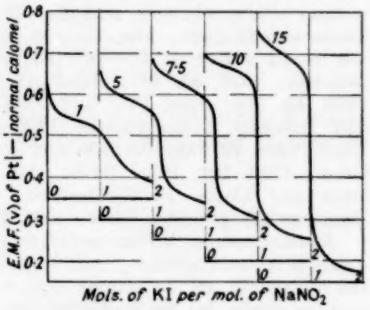


FIG. 3.



iodide at 18°. The values of *x*, *viz.*, 1—15, are marked on the respective curves. The mid-points of the inflections being taken as indicating the number of mols. of hydriodic acid that reacted with 1 mol. of nitrous acid, these values are found to be: in 1N-acid, 1·28; in 5N, 1·18; in 7·5N, 1·14; in 10N, 1·00; and in 15N, 1·00. Hence in 10—15N-solutions of sulphuric acid, nitrous acid is quantitatively reduced according to equation (1) to nitric oxide by hydriodic acid, whereas lower concentrations of sulphuric acid lead to the production of some nitrous oxide as well through the reaction of some hydriodic acid with nitrous acid, according to equation (2).

DISCUSSION

Neither the redox curves of the sulphuric acid solutions of nitrous acid in Fig. 3 nor the first three curves referring to 0·27—0·82N-hydrochloric acid solutions in Fig. 2 are divided into two sections. The two curves for 2·5N-hydrochloric acid, however, are clearly thus divided, the first section terminating when slightly less than 0·5 mol. of iodide had been added. The higher concentrations of hydrochloric acid, 5 and 7·5N, cause the initial sections to be quite well defined with almost vertical inflections with 0·5 mol. of potassium iodide. As the first 0·5 mol. of potassium iodide was added, the solutions acquired the pale yellow colour of iodine monochloride but immediately after the inflections the orange-red colour of iodine appeared. The first sections of the 5N and the 7·5N curve can therefore be explained by the equation (3), and the second sections by (4).

Unlike the interaction of nitrous and hydriodic acids in fairly concentrated sulphuric acid solutions, equation (1) provides no information regarding the mechanism of the interaction in the presence of hydrochloric acid; in this case equation (1) is composite in that it represents the sum of the two successive reactions (3) and (4). In 2·5N-hydrochloric acid some iodine monochloride is formed as judged from the pale yellow colour during the

first part of the titration ending with rather less than 0·5 mol. of potassium iodide. It thus appears that at this concentration the total reaction consists of reactions given by equations (1), (2), (3), and (4).

WASHINGTON SINGER LABORATORIES,
UNIVERSITY COLLEGE, EXETER.

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748. *The Kinetics of the Oxidation of Methane by Nitrous Oxide.*

By P. L. ROBINSON and E. J. SMITH.

The slow non-inflammatory combustion of methane in nitrous oxide at about one atmosphere total pressure has been investigated. Carbon monoxide, carbon dioxide, and water vapour are the main products in a reaction which we find has two readily recognisable stages: (*a*) $CH_4 + 3N_2O \longrightarrow CO + 2H_2O + 3N_2$; (*b*) $CO + N_2O \longrightarrow CO_2 + N_2$. Each of these must be built up of a number of consecutive steps, involving free atoms and radicals, and the chain character of the process has been demonstrated.

Rate measurements support the idea that the reaction is initiated by oxygen atoms from the thermal decomposition of nitrous oxide, and the observed activation energies are in agreement with this. The kinetics are consistent with a chain termination which is of first order with respect to the carrier concentration: the terminating step is probably $OH + N_2O \longrightarrow HO_2 + N_2$.

A reaction mechanism is advanced and discussed.

LITTLE attention has been paid to slow oxidation by nitrous oxide. Twenty years ago Melville (*Proc. Roy. Soc.*, 1933, *A*, **142**, 524; *ibid.*, 1934, *A*, **146**, 737) studied its reaction with hydrogen and, somewhat later, Bawn that with carbon monoxide (*Trans. Faraday Soc.*, 1935, **31**, 461); Steacie and MacDonald (*Canad. J. Res.*, 1935, **12**, 711) reported certain qualitative observations. So far as we know, the present work, begun four years ago, describes the first investigation of the slow oxidation of methane. Last year (Bridson-Jones, Buckley, Cross, and Driver, *J.*, 1951, 2999; Bridson-Jones and Buckley, *ibid.*, p. 3009; Buckley and Levey, *ibid.*, p. 3016) found no reaction between nitrous oxide and *n*-hexane or *cyclo*paraffins at 200—400°/2000 atm., although controlled oxidation of olefins occurred readily under these conditions.

Oxidation by nitrous oxide is closely related to its thermal dissociation, which has been extensively studied (see Hinshelwood, "Kinetics of Chemical Change," Oxford Univ. Press, 1940). Decomposition is measurable above 600°, the reaction, with increase of pressure, changing from second to first order in accordance with Lindemann's collision theory of unimolecular processes. At our pressures, the apparent order is about 1·6; thus bimolecular activation, succeeded by unimolecular dissociation, is a significant feature of the decompositions:

$$2N_2O \longrightarrow N_2O^* + N_2O$$
$$N_2O^* \longrightarrow N_2 + O\ [\longrightarrow O_2]$$

Melville (*loc. cit.*) showed that hydrogen is not oxidised until thermal dissociation of the nitrous oxide is occurring, pointing to an initiating step involving oxygen atoms, and that, once started, the rate of oxygen consumption is far greater than that provided by dissociation, indicating a direct participation of the nitrous oxide molecules. Melville postulated the sequence

$$N_2O^* \longrightarrow N_2 + O$$
$$O + H_2 \longrightarrow OH + H$$

followed by the chain

$$H + N_2O \longrightarrow OH + N_2$$
$$OH + H_2 \longrightarrow H_2O + H$$

Fennimore and Kelso's examination of the explosive reaction (*J. Amer. Chem. Soc.*, **1949, 71, 3706**) supports the idea that molecular oxygen plays no part in the slow reaction (see below).

The oxidation of carbon monoxide begins as a surface reaction which passes to an explosive one at higher temperatures and pressures, and Bawn (*loc. cit.*) has ascribed the initiation of the explosion to oxygen atoms. The high temperatures necessary (Steacie and MacDonald, *loc. cit.*) for the oxidation of carbon disulphide, and the spectroscopic evidence of atomic oxygen in nitrous oxide flames suggest that $N_2O \longrightarrow N_2 + O$ precedes the initiation of combustion.

Our study of the slow, non-inflammatory, oxidation of methane by nitrous oxide shows it to be similar to that of hydrogen: we believe it is initiated by oxygen atoms and know that it then proceeds by the direct intervention of nitrous oxide itself. No low-temperature ignition, as observed with molecular oxygen and higher paraffins, and ascribable to the formation of peroxides, appears when nitrous oxide is used; and there is no evidence of molecular oxygen's functioning as such in nitrous oxide oxidations. Once started, the reaction with methane proceeds, doubtless, by many steps which fall into two readily recognisable stoicheiometrical stages: the first producing carbon monoxide,

$$CH_4 + 3N_2O \longrightarrow CO + 2H_2O + 3N_2 \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and the second converting the carbon monoxide into dioxide,

$$CO + N_2O \longrightarrow CO_2 + N_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In both stages, the rapid consecutive steps must be of a chain character in which atoms and radicals participate; and, as might be expected, under more severe conditions the oxidation becomes explosive.

We have found the rate of the slow oxidation to depend mainly on the concentration of nitrous oxide and relatively slightly on that of methane; and the activation energy of the oxidation to be significantly close to that of the decomposition of nitrous oxide alone. The kinetics are consistent with a chain-terminating step which is of first order with respect to carrier concentration, and we advance reasons for supposing that step to be $OH + N_2O \longrightarrow HO_2 + N_2$. A mechanism which would account for the present observations is described.

Experimental

Materials.—(a) *Methane.* Natural gas, from a cylinder, was passed over copper oxide at 310° to oxidise hydrogen and carbon monoxide, over " Carbosorb " to remove carbon dioxide, and through two spiral washers containing alkaline pyrogallol to remove oxygen. After being dried (P_2O_5), it was condensed and distilled four times, with rejection of head and tail fractions on each occasion. It was kept in glass reservoirs.

(b) *Nitrous oxide.* Commercial gas was washed with alkaline pyrogallol and dried (P_2O_5). It was frozen and all gaseous residue was removed by pumping. The solid was repeatedly just melted and refrozen, occluded or adsorbed gas being pumped off each time. It was stored, either at a low temperature as solid, or as gas in glass reservoirs.

(c) *Nitrogen.* Commercial gas was washed with alkaline pyrogallol and passed over freshly reduced copper gauze, at 550°, to remove oxygen. It was dried (P_2O_5) and delivered directly to the reaction vessel.

Apparatus.—The reaction was carried out in clear, cylindrical, silica vessels, packed and otherwise, which had capillary necks, of 2-mm. bore, terminating in standard ground joints.

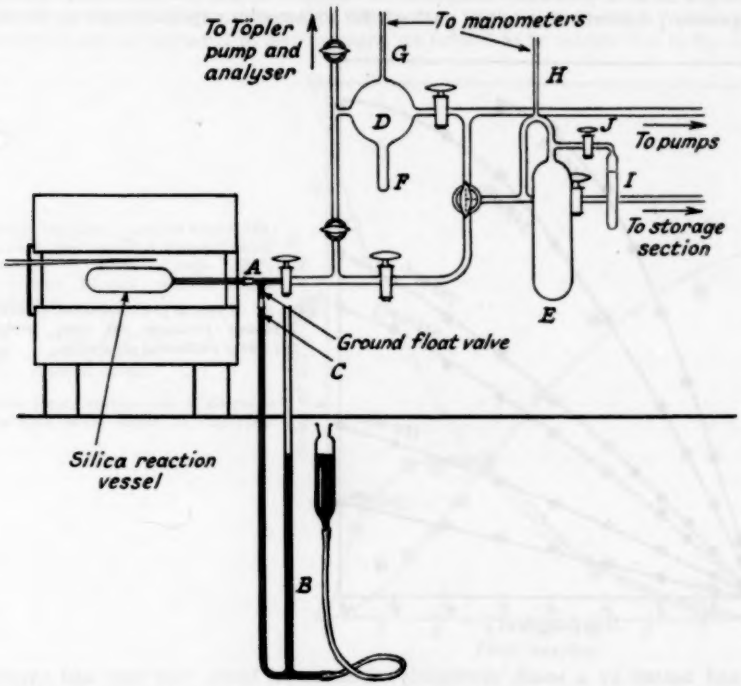
Vessel	Dimensions, cm.	Surface/vol. ratio
Large (unpacked)	13·5 × 2·8	1·51
Large (packed)	13·5 × 2·8	11·30
Medium	12·0 × 1·9	2·33
Small	12·5 × 0·9	4·50

Before being first used, and later periodically, they were treated with " AnalaR " hydrofluoric acid (10%) for 15 minutes, and thoroughly washed with distilled water. This left the silica surface without visible etching, and capable, after a number of runs, of giving reproducible results. This conditioning by operation was marked by a decrease in rate which we attribute

to increase in the chain-breaking properties of the surface. The temperature of the tubular furnace was semi-automatically controlled by a Sunvic energy regulator and hot-wire switch, and measured by means of a Pt–Pt–Rh thermocouple and Cambridge auto-C.J. indicator. Temperatures varied by less than 2° over the operative length of the furnace and could be maintained within 1° for many hours.

The reaction vessel led through its ground joint *A* (Fig. 1), sealed with picein, to the constant-volume manometer *B*, in which the mercury was kept at a fixed point *C*; to the quenching vessel *D*, by which means a reaction could be rapidly stopped by expanding the reactants into a vacuum; and to the mixing chamber *E*. The " quencher," furnished with a prolongation *F*, in which material might be condensed, led to the analysis section. The " mixer " was in direct connection with the storage section. Two supplementary manometers, *G* and *H*, made for

FIG. 1.



convenience in manipulation. There was also a " doser " (not shown in Fig. 1) coupled to the " mixer " which allowed runs with a given mixture to be repeated several times. The tubing connecting the reaction vessel and manometer *B* was electrically heated to about 65° to prevent condensation of water vapour produced in the reaction. Evacuation was by a Kaye-type mercury-vapour pump, backed by a Speedivac rotary oil pump.

The analytical system consisted of a Töpler pump, to transfer the gas from the reaction and quenching vessels, after the carbon dioxide and the residual nitrous oxide had first been condensed by cooling the prolongation on the " quencher," and the spiral trap on the inlet side of the Töpler pump to −180°. This separation simplified the analysis and is necessary because of the appreciable solubility of nitrous oxide in the aqueous absorbents. The gases were passed to a calibrated gas burette (capacity 10 c.c.; graduations 0·01 c.c.), surrounded by a water-jacket and communicating, through a three-way capillary-bore tap, with absorption and combustion pipettes, and with sources of nitrogen and oxygen. A small dead space above the zero mark of the burette was filled with nitrogen before every analysis. The gases were kept saturated with water vapour during the estimations. Each 10-c.c., cylindrical, absorption pipette had an adjustable reservoir, so that, when absorption was complete, the liquid could be

restored to the fixed mark. The reagents used were 40% potassium hydroxide and alkaline pyrogallol solutions. The determination of carbon monoxide in the presence of methane was troublesome at first: combustion on a platinum spiral was not sufficiently specific in the presence of considerable amounts of methane. Methods involving the selective oxidation of carbon monoxide on metallic oxide catalysts were then tried. Of these, copper oxide gives a satisfactory response but requires a temperature of 300°. " Hopcalite " (a material containing oxides of copper, manganese, cobalt, and silver) was more attractive because of its higher specificity and lower operating temperature. It commences to oxidise carbon monoxide at room temperature but does not do this quantitatively, as others have observed (Thomas, Dunn, and Levin, *Analyt. Chem.*, 1949, **21**, 1476). We found, however, that, when " Hopcalite " is maintained at 100°, rapid, quantitative oxidation even of high concentrations of carbon monoxide ensues and methane is unaffected; but, since the catalyst readily absorbs oxygen at 100°, this gas must be previously removed. A simple arrangement, consisting of a few pellets of " Hopcalite " located in a wider part of the (otherwise) capillary lead to the hydroxide

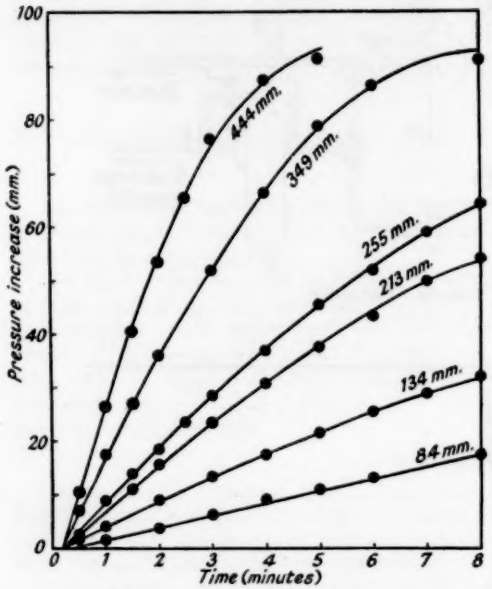


FIG. 2. *Typical pressure–time records for* 666°. *Methane pressure* 50 *mm., nitrous oxide pressures indicated on curves.*

pipette and heated by a small, electrically wired, metal block, was easy and expeditious in operation and gave results with a tested accuracy of about 3%. Combined with the separation by freezing mentioned above, it was adequate for the mixtures under examination. The water vapour formed in the reaction was estimated by difference: from the total pressure of gases and water vapour, the partial pressure of the gases was deducted.

Operation.—The oxidation of methane by nitrous oxide gives a pressure increase, provided that the water vapour formed is allowed to contribute; but the changes in pressure resulting from a number of consecutive stages do not show a simple correspondence to changes in composition (Figs. 2 and 3). Hence, manometric observations were supplemented by chemical analysis. The proportionation of the reactants was done by admitting the nitrous oxide to *E*, measuring its pressure on manometer *H*, freezing it in *I*, and isolating the solid by closing tap *J*. The second compound was then admitted, and its pressure measured. Finally, tap *J* was opened and the gases were allowed to mix by diffusion for 5 hours or more. This procedure gave mixtures of precisely known composition, and avoided diffusion of the first component towards the storage vessel on admission of the second gas. Between runs, the reaction vessel, maintained at the working temperature, was evacuated for a standard period of 15 minutes.

As a test of apparatus and manipulation, certain of Melville's experiments on hydrogen were repeated with, incidentally, complete confirmation of his findings. The water vapour produced

was absorbed immediately outside the reaction vessel by phosphoric oxide, so that the combined pressures observed were due to hydrogen, nitrous oxide, and nitrogen: $H_2 + N_2O \longrightarrow H_2O + N_2$.

Measurements.—Analysis disclosed the two main stages (1) and (2) (p. 3896). Fig. 3 gives composition–time curves for mixtures having initial pressures of methane 40 mm., and nitrous oxide 160 mm., heated at 725°. It shows, initially, a close relation between the nitrous oxide used and the carbon monoxide produced. Precise measurement of the amounts of carbon dioxide produced in the early stages of the reaction is difficult, but it seems reasonable to extrapolate the curve showing its formation to zero time, asymptotically, since its rate of formation clearly depends on the concentration of carbon monoxide. Therefore the initial portions of the curves in Figs. 2 and 3 are taken as referring to stage (1) alone. A flattening of the pressure–time curves (Fig. 2), in a direction parallel to the time axis, occurs later and is ascribed in part to the intervention of stage (2) which does not itself involve an alteration in pressure, and in part to the consumption of the reactants. The slight induction periods evident when these curves are extrapolated to zero pressure, we believe to be mainly due to the interval

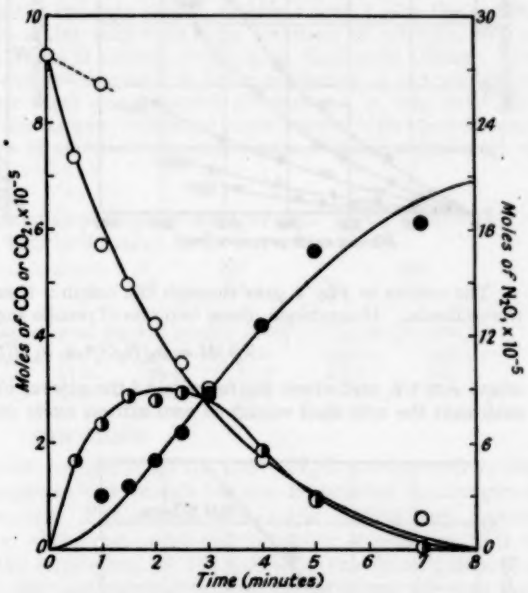


FIG. 3. *Analytical data: carbon monoxide, carbon dioxide, and residual nitrous oxide after intervals of time. Temp. 725°, methane pressure 40 mm., nitrous oxide pressure 160 mm.*

◑ *Carbon monoxide.*
● *Carbon dioxide.*
○ *Nitrous oxide.*

Broken line shows initial rate of decomposition of nitrous oxide alone at 725°/160 mm.

during which the reactants reach the starting temperature. From that point the reaction accelerates rapidly to its maximum rate; and the pressure–time curves have not the marked sigmoid form, so characteristic of the slow oxidation of hydrocarbons by molecular oxygen and ascribed to degenerate chain-branching.

Attempts at a quantitative determination of the more stable intermediate species were not made; but our qualitative observations, derived from a streaming system, are worth recording. Formaldehyde, indicated by Schiff's test, was obtained in sufficient amount to afford a crystalline derivative with dimedone, m. p. 187° (lit., 189°). Some cyanide and nitrite could be extracted from the effluent gases when these were bubbled through water, the nitrite being particularly prominent for mixtures rich in nitrous oxide and also for normal mixtures subjected to higher temperatures.

For comparison, Fig. 3 also shows the initial rate of the homogeneous decomposition of nitrous oxide alone, at the same temperature and pressure: the rate is about one-seventh of the rate of the reaction with methane measured in terms of consumption of nitrous oxide.

The effect, on the initial rate of the reaction, as expressed in pressure change in mm./min., of independently varying the nitrous oxide and methane partial pressures is shown in Fig. 4, wherein the starting pressure of methane is 50 mm. throughout and the temperatures 609—

685°; and in Fig. 5, wherein the starting pressure of nitrous oxide is 50 mm. and the temperature 665—725°. Evidently, the order with respect to nitrous oxide is greater than unity, and is proved, by reference to the parallel logarithmic plots obtained by using the data in Fig. 5, to be about 1·6. Independent experiments on the rates of decomposition of nitrous oxide alone, in the same pressure and temperature range, gave an identical value, 1·6.

FIG. 4. *Influence of nitrous oxide pressure on initial rate, constant methane pressure = 50 mm.*

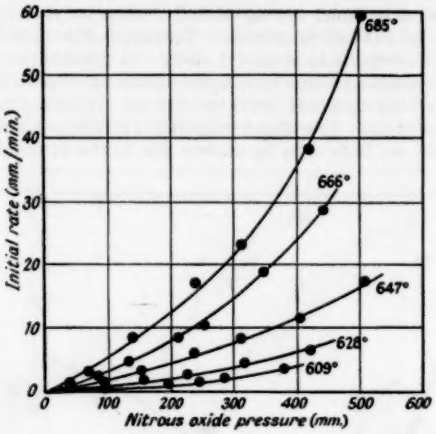
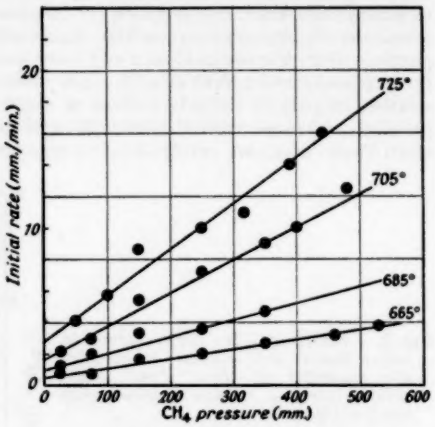


FIG. 5. *Influence of methane pressure on initial rate, constant nitrous oxide pressure = 50 mm.*



The curves in Fig. 4 pass through the origin: those in Fig. 5 make positive intercepts on the ordinate. If combined, these two sets of results suggest a rate equation of the form,

$$dp/dt = k_1[N_2O]^x + k_2 f([N_2O])[CH_4] \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $x \simeq 1{\cdot}6$, and where the function of the nitrous oxide concentration in the second term is such that the rate shall vanish at zero nitrous oxide pressure, as required by the experimental

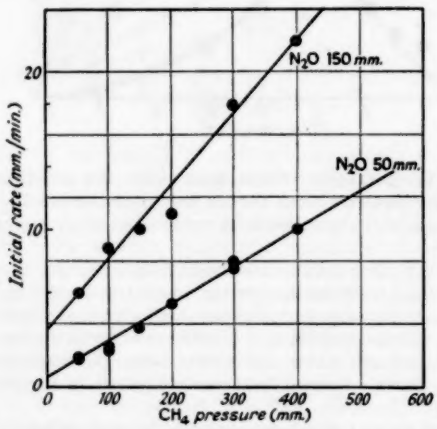


FIG. 6. *Influence of methane pressure on initial rate at 665° at invariant nitrous oxide pressures of 50 mm. and 150 mm.*

facts in Fig. 4. This function may be found, approximately, from the data in Fig. 6, *viz.*, the plots of initial rates against methane pressure for invariant nitrous oxide pressure of 50 mm. and 150 mm., respectively, at 665°. Equation (3) requires the intercepts on the ordinate to equal $k_1[N_2O]^{1\cdot6}$, and the slopes to vary as $f([N_2O])$. The intercepts show the required agreement. Comparison of the slopes shows $f([N_2O])$ to be respresentable by $[N_2O]$ to a power below

unity, since a three-fold increase in $[N_2O]$ increases the slope by a factor of 2, and $f([N_2O]) \simeq [N_2O]^{<1}$. Hence the empirical rate equation (3) becomes more precisely

$$dp/dt = k_1[N_2O]^x + k_2[N_2O]^y[CH_4] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where $x \simeq 1{\cdot}6$ and $y \simeq 0{\cdot}65$.

The constants k_1 and k_2 are both sensitive to temperature, since the intercepts and slopes in Fig. 5 which are proportional to k_1 and k_2, respectively, increase with temperature. By plotting the natural logarithms of the slope against the reciprocal of the absolute temperature, as required by the Arrhenius equation, an activation energy of 50 kcal. was deduced from the temperature dependence of rate constant k_2. Similar treatment of the intercepts gave an activation energy of about 53 kcal. from the temperature dependence of k_1.

Since present knowledge of the oxidations of hydrocarbons and the temperatures at which they take place makes reaction chains probable, experiments were done in the presence of an inert gas and also in packed vessels. If deactivation of the chain-carriers at the surface occurred, an inert gas would, by impeding the diffusion of carriers to the walls, be expected to lead to an increase in the observed rate of reaction. Conversely, packing of the reaction vessel, by shortening the chains, would have the opposite effect. Tables 1 and 2 give the results obtained, and show a definite increase in the rate with large additions of nitrogen, and a noticeable decrease when the reaction vessel is packed with 5-mm. silica quill tubing. The influence of surface on reaction rates also reveals itself in the conditioning of the vessels by operation (see above) and is observable when measurements are repeated at long intervals. For this reason, particular sets of experiments were completed consecutively, with the minimum of interval of time and the employment of standard pumping times. The reproducibility of rates in a given series was better than 5%.

TABLE 1. *Initial rates in absence and in presence of nitrogen* (685°; $CH_4 = 25$ *mm.*, $N_2O = 75$ *mm.*).

Nitrogen (mm.)	0	337	0	433
Initial rate (mm./min.)	5·2	7·4	4·8	7·0

TABLE 2. *Initial rates in unpacked and packed vessels* (686°; $CH_4 = 50$ *mm.*).

N_2O, mm.	400	350	270	200	100
Initial rate, mm./min. unpacked	37·0	29·0	21·0	13·8	5·0
Initial rate, mm./min. packed	26·5	21·0	13·3	9·8	3·3

DISCUSSION

Initiation of the oxidation by atomic oxygen from the fission N_2O is suggested by the fact that it occurs only above a temperature high enough for this dissociation to take place, and is supported by the observed kinetics. Equation (4) reflects the finding that the rate depends mainly on the concentration of nitrous oxide and relatively slightly on that of methane. Its first term resembles the expression for the homogeneous decomposition of nitrous oxide, measurable just above 600° and varying in order between two, for very low, and one, for about 40 atm. pressure. The change in order indicates activation of the nitrous oxide molecules in binary collisions, followed either by deactivation in a subsequent collision or by unimolecular decomposition :

$$2N_2O \longrightarrow N_2O + N_2O^* \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$N_2O^* + N_2O \longrightarrow 2N_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$N_2O^* \longrightarrow N_2 + O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$O + O + M \longrightarrow O_2 + M \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

$$O + N_2O \longrightarrow O_2 + N_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

$$-d[N_2O]/dt = k_5[N_2O]^2/(1 + (k_6/k_7)[N_2O]) \quad . \quad . \quad . \quad . \quad . \quad (10)$$

(A rate constant carries the serial number of the equation to which it refers.)

Reactions (8) and (9) are assumed to be very fast. Admittedly this is an over-simplification since it admits only one mode of excitation (Hinshelwood, *op. cit.*; Hinshelwood and Stubbs, *Discuss. Faraday Soc.*, Hydrocarbons, 1951) but it is in the main true. It predicts an apparent order which is a continuous function of pressure and lies between two and one,

in broad agreement with experiment. In the range 100—500 mm. we find an apparent order of about 1·6, making the first term in the oxidation equation (4) identical, apart from a numerical constant, with the sole term in the decomposition equation (10). The reactions have closely similar activation energies. These facts support the hypothesis that the oxidation is initiated by atomic oxygen and suggest that the term $k_1[N_2O]^{1\cdot6}$ might be replaced by $k_1'k_5[N_2O]^2/(1 + (k_6/k_7)[N_2O])$, in which k_1' is a numerical constant. Direct evidence of oxygen atoms at the temperatures used is difficult to obtain, but Whittingham (*Nature*, 1947, **159**, 232) has identified the luminous decomposition of nitrous oxide at about 900° with the continuous emission produced during the combination of atomic oxygen and nitric oxide (Gaydon, *Trans. Faraday Soc.*, 1946, **42**, 293). Steacie and Parlee (*Canad. J. Res.*, 1938, **16**, *B*, 203) have shown that oxygen atoms react readily with methane and have estimated the activation energy to be *ca.* 8 kcal. per mole. No mechanism was given, but the most plausible initial step would appear to be

$$CH_4 + O \longrightarrow CH_3 + OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

In the oxidation of methane by nitrous oxide, step (11) is consequential on the dissociation (7). An alternative initiation, involving molecular oxygen, $CH_4 + O_2 \longrightarrow CH_3 + HO_2$, although not precluded by the kinetics, would require an activation energy much greater than 8 kcal. and is discounted. No evidence has been obtained, either phenomenal or analytical, of the presence of molecular oxygen at any stage. If present, it was certainly less than 0·25 mole % at 725°. From that point, the evidence suggests a chain mechanism; and a comparison of the rates of the oxidation and the dissociation reaction suggests a mean chain length, in terms of nitrous oxide molecules, of about 7. The kinetics may be explained, as far as the carbon monoxide stage, in terms of the chain mechanism continuing from reaction (11) in the following manner:

$$OH + CH_4 \longrightarrow H_2O + CH_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

$$CH_3 + N_2O \longrightarrow CH_3{\cdot}O + N_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

$$CH_3{\cdot}O \longrightarrow H{\cdot}CHO + H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

$$H + N_2O \longrightarrow OH + N_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

$$H{\cdot}CHO + N_2O \longrightarrow CO + H_2O + N_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

$$N_2O + OH \longrightarrow HO_2 + N_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

We recognise that this scheme is not free from ambiquity; the explicit study of some of the elementary steps may modify the postulated pattern.

The propagation step (12) appears indisputable and has been ascribed an activation energy of 8·5 kcal. (van Tiggelen, *Ann. Mines Belg.*, 1942, **43**, 117; quoted by Steacie, "Atomic and Free Radical Reactions," 1946). We have chosen to represent the formation of formaldehyde by the consecutive stages (13) and (14), rather than by the direct step, $CH_3 + N_2O \longrightarrow H{\cdot}CHO + N_2$, since the breakdown of alkoxyl radicals to carbonyl compounds (14), is well established, as is also the relatively high stability of the methoxyl radical (Milas and Surgenor, *J. Amer. Chem. Soc.*, 1946, **68**, 205; George and Walsh, *Trans. Faraday Soc.*, 1946, **42**, 94; Raley, Rust, and Vaughan, *J. Amer. Chem. Soc.*, 1948, **70**, 88, 95; Rust, Seubold, and Vaughan, *ibid.*, 1950, **72**, 338). The rôle of formaldehyde has not been ascertained, but it is probably always an intermediate of importance in the oxidative degradation of methane (Norrish, *Discuss. Faraday Soc.*, Hydrocarbons, 1951).

Some chain-terminating step keeps the hydroxyl-radical concentration finite, since a sudden approach to an explosion region is not observed. As the deactivation of hydroxyl radicals on a surface is not feasible at our pressures, there remain only two possible, homogeneous steps, *viz.*, (17) and the bimolecular recombination

$$2OH + M \longrightarrow H_2O_2 + M \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

M being a third body necessary to stabilise the H_2O_2 molecule on formation. Reaction (18) leads to a second term in the theoretical rate equation (22) at variance with experiment and is less likely because of the lower frequency of bimolecular collisions, whereas reaction (17) is in accordance with our kinetics. The latter accounts, by virtue of the surface destruction

of the HO_2 radicals, for the fall in rate observed when the surface/volume ratio is increased. This formation and surface destruction of the HO_2 radical has been frequently invoked as a chain-terminating step: typical examples are in the hydrogen–oxygen reaction, where its formation in ternary collisions accounts for the second explosion limit (Hinshelwood, *op. cit.*; Lewis and von Elbe, *J. Chem. Physics*, 1942, **10**, 366), the inhibition of the hydrogen–chlorine reaction by oxygen (Bodenstein and Schenk, *Z. physikal. Chem.*, 1933, *B*, **20**, 420; Norrish and Ritchie, *Proc. Roy. Soc.*, 1933, *A*, **140**, 713), and in the hydrogen–nitrous oxide reaction at high temperatures. In connection with the last, Fennimore and Kelso (*loc. cit.*) have shown that, above 850°, the explosion pressure for a mixture of nitrous oxide and hydrogen has a negative temperature coefficient, a peculiarity which they ascribe to the deactivation of hydrogen atom chain-carriers by oxgyen molecules, formed through the rapid dissociation of nitrous oxide at this temperature. The reaction, $H + O_2 + M \longrightarrow HO_2 + M$, produces this relatively stable radical which does not propagate chains with the facility of either the hydroxyl or the hydrogen atom.

The stability of the HO_2 radical has been considered by Minkoff (*Discuss. Faraday Soc.*, The Labile Molecule, 1947) and by Walsh (*J.*, 331, 1948) who says its heat of formation may be as high as 60 kcals. Electron-impact studies on hydrogen peroxide by Robertson (*Trans. Faraday Soc.*, 1952, **48**, 228) give the heat of the reaction, $H + O_2 \longrightarrow HO_2$ as 46 ± 9 kcal. which is closer to the earlier estimates of 40 kcal. (Bodenstein and Schenk, *loc. cit.*) and 50 kcal. (Haber and Weiss, *Proc. Roy. Soc.*, 1934, *A*, **147**, 350).

If we take the value as 50 kcal., and the bond-dissociation energies of the oxygen molecule as 118 kcal. (Gaydon, " Dissociation Energies," Chapman and Hall), of the OH radical as 100 kcal. (Dwyer and Oldenberg, *J. Chem. Physics*, 1944, **12**, 351), and of the N–O bond in N_2O as 55 kcal., the heat of reaction (17) must be about 13 kcal. Therefore, at our temperature the reaction is thermodynamically acceptable; and, moreover, the simultaneous ejection of molecular nitrogen in the binary collisions predisposes towards stabilised HO_2 radicals. It is thus unnecessary to invoke a terminating step depending on triple collisions. The stabilised HO_2 radicals have a relatively high probability of surviving until they reach a surface.

The following rate equation may be deduced, if the usual simplifying assumption is made that the concentrations of the respective atoms, radicals, and formaldehyde become stationary once the reaction has been started. This we believe to be true of formaldehyde despite its being found in some quantity in the streaming experiments where the amounts of material involved are much larger.

$$\frac{dp}{dt} = \frac{3k_5[N_2O]^2}{1 + (k_6/k_7)[N_2O]} + \frac{4k_5k_{12}}{k_{17}} \times \frac{[N_2O][CH_4]}{1 + (k_6/k_7)[N_2O]} \quad . \quad . \quad . \quad (21)$$

or

$$dp/dt = 3k_5[N_2O]^{1\cdot6} + 4(k_5k_{12}/k_{17})[N_2O]^{0\cdot6}[CH_4] \quad . \quad . \quad . \quad . \quad (22)$$

This shows close similarity with the empirical rate equation. The empirical rate constant k_1 is identified with $3k_5$, and the activation energy, derived from temperature variation of k_1, is confirmed as being the same as that for the decomposition of nitrous oxide alone; k_2 corresponds to the composite constant k_5k_{12}/k_{17}, and hence the activation energy deduced from the slopes in Fig. 6 must be $(E_5 + E_{12} - E_{17})$. Since $(E_5 + E_{12} - E_{17}) \simeq 50$ kcal., $E_5 \simeq 55$ kcal., and $E_{12} = 8\cdot5$ kcal., E_{17} must be about 13·5 kcal. The fact that the second term makes a relatively small contribution to the total rate implies a difference between the frequency factors of reactions (12) and (17), that of (12) being lower by at least a power of 10.

If the bimolecular terminating reaction, $2OH + M \longrightarrow H_2O_2 + M$ (18), were substituted for reaction (17) the predicted initial rate of pressure rise becomes

$$\frac{dp}{dt} = \frac{k_5[N_2O]^2}{1 + (k_6/k_7)[N_2O]} + 2k_{12}\left(\frac{k_5}{k_{18}} \times \frac{2[N_2O]^2}{\{1 + (k_6/k_7)[N_2O]\}[M]}\right)^{\frac{1}{2}}[CH_4]$$

where $M = N_2O + CH_4$.

If methane functioned effectively as a third body in (18), a progressive decrease in the order with respect to methane would follow a rise in its concentration, but the data expressed in Fig. 5 emphatically contradict this. Furthermore, in these circumstances the temperature dependence of k_2 would yield an activation energy equal to $(\frac{1}{2}E_5 + E_{12} - \frac{1}{2}E_{18})$, or about 33 kcal., in place of the 50 kcal. found. The available evidence is, in our opinion, definitely against a predominantly bimolecular termination.

The oxidation of carbon monoxide, stoicheiometrically represented by equation (2), evidently proceeds at a similar rate to the oxidation of methane by which it is produced. It takes place under conditions approximating to those in which an explosive reaction was observed by Bawn (*loc. cit.*). But, in addition to the energy chain suggested by that author when only nitrous oxide and carbon monoxide were present, there are at least two other possible processes of oxidation: first, by atomic oxygen, $CO + O \longrightarrow CO_2$, and, secondly, by hydroxyl, $OH + CO \longrightarrow CO_2 + H$. In both, carbon monoxide would be competing for species necessary to the continuance of the chain reaction responsible for its own formation, a feature which would result in its concentration reaching a stationary value, as we have found.

The authors are indebted to Mr. J. H. Smith, Departmental Assistant, for assistance in the fabrication of certain of the glass and silica apparatus used, and to the Northumberland Education Committee and the Department of Scientific and Industrial Research for maintenance grants held consecutively, which enabled one of them (E. J. S.) to take part in the work.

KING'S COLLEGE, NEWCASTLE-ON-TYNE, 1. [*Received, March 8th*, 1952.]

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749. *The Chemistry of the* Mitragyna *Genus. Part III.* Synthesis of a Degradation Product of Mitragynine.*

By J. W. COOK, J. D. LOUDON, and P. MCCLOSKEY.

Derivatives of 2 : 3-dihydro-3-ketobenz-1 : 4-oxazine were produced by heating α-halogenoacyl-*o*-anisidides with aluminium chloride at 160—190°. At a higher temperature 2 : 3-dihydro-3-keto-4-methylbenz-1 : 4-oxazine underwent rearrangement, and methylation of the phenolic product afforded a mixture of 4- and 7-methoxy-1-methyloxindoles. These oxindoles were reduced by lithium aluminium hydride to the corresponding indoles, and their structures were established by independent, standard syntheses.

4-Methoxy-1-methylindole was converted *via* the corresponding gramine and tryptophan into 6-methoxy-1 : 2-dimethyl-β-carboline (IX). This was shown to be identical with the degradation product of mitragynine, which Ing and Raison obtained by distillation of the alkaloid from zinc dust (*J.*, 1939, 986).

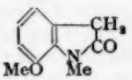
ING and RAISON (*J.*, 1939, 986) pointed out that the base, $C_{14}H_{14}ON_2$, which they obtained by degrading the alkaloid mitragynine, has the properties of a methoxy-*N*-methylharman. They showed, however, that it was not identical with *ind*-*N*-methylharmine (8-methoxy-1 : 2-dimethyl-β-carboline †) and Cook, Loudon, and McCloskey further showed that it was distinct from 7-methoxy-1 : 2-dimethyl-β-carboline (Part II*). None the less the close resemblance of the degradation product to these isomeric bases encouraged the view that the compound is indeed an *ind*-*N*-methylharman and we now present evidence which establishes its structure.

Since the alkaloid vomicine is known to contain an indole fragment which is oxygenated at position-7, corresponding to position-9 of the β-carboline system, and since damascenine (methyl 3-methoxy-2-methylaminobenzoate) might be considered as biogenetically related to a 7-methoxy-1-methylindole, our attention was primarily directed to the synthesis of 9-methoxy-1 : 2-dimethyl-β-carboline. In view of the inaccessibility of 7-methoxyindole the preparation of 7-methoxy-1-methyloxindole (I) by the Stollé method was attempted. This involved heating the chloroacetyl derivative of *N*-methyl-*o*-anisidine with aluminium chloride at 160° and, not unexpectedly, the main product of the reaction was the benzoxazine

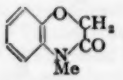
* Part II, *J.*, 1951, 1203. † Numbering as in (IX).

derivative (II). As had been hoped, however, this compound was converted by aluminium chloride at higher temperatures into derivatives of indole. The alkali-soluble rearrangement product was not homogeneous but, after methylation with methyl sulphate and alkali, was converted into two isomeric methoxyoxindoles (A) and (B) of molecular formula $C_{10}H_{11}O_2N$. On reduction with lithium aluminium hydride each compound yielded a corresponding methoxyindole together with a methoxyindoline, but whereas oxindole-A and its reduction products—indole-A and indoline-A—were readily shown to contain each one *N*-methyl group, the *N*-methyl value determined for oxindole-B was fractional and was zero for indole-B and for the picrate of indoline-B. Since Ing and Raison's compound is known to contain one *N*-methyl group, indole-A was here selected for successive conversion into the corresponding gramine, tryptophan, and methoxy-1 : 2-dimethyl-β-carboline by reactions which are more fully described below. The carboline thus synthesised proved to be identical with the mitragynine degradation product.

At this stage, therefore, it seemed highly probable that the degradation product of mitragynine was 9-methoxy-1 : 2-dimethyl-β-carboline although the situation was somewhat anomalous in that the synthesis did not provide unequivocal proof of structure. Nevertheless the remaining ambiguity was now associated with compounds of simpler type and attention was turned to identifying 7-methoxy-1-methylindole by an independent and unambiguous synthesis. Methylation of 7-methoxyindole by the action of methyl iodide and potassium in liquid ammonia afforded a methylated product which was identified as indole-B and, like the original specimen, gave a zero value for *N*-methyl analysis. This result suggested that *C*-methylation had occurred but the compound was then found to be isomeric and not identical with either 7-methoxy-2- or -3-methylindole. These compounds were synthesised by the Fischer method from the *o*-methoxyphenylhydrazones of acetone and propaldehyde respectively. Furthermore *N*-methyl-*o*-anisidine was acylated by oxalyl chloride and the product (III) was smoothly converted into 7-methoxy-1-methylisatin (IV) by aluminium chloride in ethylene dichloride. Reduction of (IV) in two stages gave oxindole-B.



(I)



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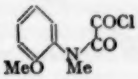

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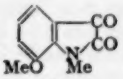


(IV)

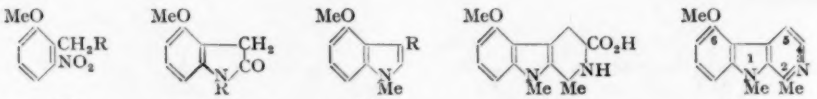
In the light of these findings the conclusion was inescapable that indole-B and oxindole-B are 7-methoxy-1-methyl-indole and -oxindole (cf. I) respectively, and that in consequence Ing and Raison's compound cannot be 9-methoxy-1 : 2-dimethyl-β-carboline. The elimination of the 7-, 8-, and 9-methoxy-1 : 2-dimethyl-β-carboline structures, when considered together with the synthesis of the mitragynine degradation product as outlined above, virtually identifies the compound as 6-methoxy-1 : 2-dimethyl-β-carboline (IX). Confirmation was now sought in an unambiguous synthesis of oxindole-A which, accordingly, should be 4-methoxy-1-methyloxindole. To this end 2-methoxy-6-nitrobenzyl chloride (V; R = Cl) was condensed with potassium cyanide in aqueous ethanol and the nitrile formed was hydrolysed to 2-methoxy-6-nitrophenylacetic acid (V; R = CO_2H). Catalytic reduction of this acid was accompanied by cyclisation of the intermediate amino-acid with formation of 4-methoxyoxindole (VI; R = H) and methylation then yielded 4-methoxy-1-methyloxindole (VI; R = Me) which was found to be identical with oxindole-A.

It follows from the identification of oxindole-A that indole-A is 4-methoxy-1-methylindole (VII; R = H) and its conversion into the mitragynine degradation product may now be described more fully. Condensation of the indole (VII; R = H) with formaldehyde and dimethylamine gave 4-methoxy-1-methylgramine (VII; R = $CH_2 \cdot NMe_2$) (conveniently characterised as the picrate). In the form of its methiodide, this reacted with ethyl sodioacetamidomalonate, yielding [VII; R = $CH_2 \cdot C(NHAc)(CO_2Et)_2$] and thence by appropriate stepwise hydrolysis and decarboxylation 4-methoxy-1-methyltryptophan [VII; R = $CH_2 \cdot CH(NH_2) \cdot CO_2H$]. The tryptophan was condensed with acetaldehyde, forming 2 : 3 : 4 : 5-tetrahydro-6-methoxy-1 : 2-dimethyl-β-carboline-4-carboxylic acid

(VIII) from which 6-methoxy-1 : 2-dimethyl-β-carboline (IX) was obtained by treatment with potassium dichromate. The carboline (IX) was most easily purified by chromatography and the same treatment was applied to a specimen of the mitragynine degradation product. Both samples, and their picrates and *p*-nitrobenzylidene derivatives, had corresponding melting points which remained undepressed on admixture of the appropriate pairs of compounds.

Although derivatives of 5-, 6-, and 7-hydroxy- and of 5 : 6-dihydroxy-indole have been recognised among naturally occurring compounds (cf. Sir Robert Robinson, *Chem. and Ind.*, 1952, 358) this degradation product of mitragynine is the first representative of the 4-hydroxyindole type to be obtained from a natural source. It is produced, however, by distilling mitragynine with zinc dust and in view of the severity of this treatment its precise significance in respect of the alkaloid's structure requires further investigation.

The formation of oxindole-A (VI; R = Me) by methylation of the phenolic rearrangement products of 2 : 3-dihydro-3-keto-4-methylbenzoxazine (II) indicates that the latter is partly converted into 4-hydroxy-1-methyloxindole during the fusion with aluminium chloride. This involves a change—from *ortho* to *meta*—in the positional relationship between the *O*- and the *N*-atom attached to the benzene ring, and migration of one or other of them must occur. Discussion of the reaction mechanism must await fuller investigation but it may be noted here that the change was confirmed on specially purified material and that by heating 7-methoxy-1-methyloxindole with aluminium chloride, followed by methylation of the phenolic product, there was obtained only the starting compound, thereby eliminating 7-hydroxy-1-methyloxindole as a possible intermediate in the formation of the 4-hydroxy-isomer. Finally, under the conditions effective in rearranging (II), neither 2 : 3-dihydro-3-ketobenz-1 : 4-oxazine nor its 2-methyl derivative yielded appreciable quantities of phenolic material. The last two compounds were prepared by heating chloroacetyl- and α-bromopropionyl-*o*-anisidide respectively with aluminium chloride.



(V) (VI) (VII) (VIII) (IX)

The low values obtained in *N*-methyl estimations in the 7-methoxy-1-methylindole series remain unexplained. The infra-red absorption spectra of the oxindoles-A and -B resemble each other and also the corresponding spectrum of an *N*-alkyloxindole: in particular, they show that neither contains a free hydroxyl or imino-group and that a carbonyl group is present in both. It may be added that ready reduction to the corresponding indole, as here effected by lithium aluminium hydride, is more characteristic of an *N*-alkyl- than of an *N*-unsubstituted oxindole (cf. Julian and Printy, *J. Amer. Chem. Soc.*, 1949, **71**, 3206). *N*-Methyl determinations, independently carried out in other laboratories on 7-methoxy-1-methylindole, gave positive but fractional values which were subject to rather wide variation and the conclusion may be drawn that a real analytical difficulty exists. On the other hand it is noteworthy that, as recorded in the following paper, 9-methoxy-1 : 2-dimethyl-β-carboline, which contains the 7-methoxy-1-methylindole structure, gave a satisfactory combined *O*- and *N*-methyl analysis.

Experimental

M. p.s are corrected unless otherwise stated.

N-Methyl-*o*-anisidine was prepared by the action of methyl sulphate (or iodide) on the sodio-derivative of acetyl-*o*-anisidide, followed by removal of the acetyl group by refluxing 50% sulphuric acid (6 hours). It had b. p. 228—230°/760 mm., 138—139·5°/47 mm. (Diepolder, *Ber.*, 1899, **32**, 3515, gives b. p. 141—143°/46—47 mm.; Mülhäuser, *Annalen*, 1881, **207**, 247, gives b. p. 218—220°; Best, *ibid.*, 1889, **255**, 176, gives b. p. 220°). The picrate formed yellow prisms, m. p. 141—142°, from ethanol (Found: C, 45·9; H, 4·0; N, 15·4. Calc. for $C_8H_{11}ON,C_6H_3O_7N_3$: C, 45·9; H, 3·8; N, 15·3%) (Wedekind, *Ber.*, 1906, **39**, 486, gives m. p.

139°). Addition of methyl sulphate (1 mol.) to *o*-anisidine (1 mol.) at 50—60°, with subsequent warming to 80° for 1 hour, yielded, probably, mainly *NN*-dimethyl-*o*-anisidine, b. p. 128—131°/47—48 mm., 210—211°/743 mm. (Mülhäuser, *loc. cit.*, gives b. p. 210—212°). The *picrate* formed yellow prisms, m. p. 144—145°, from ethanol (Found: C, 47·2; H, 4·4; N, 14·8. $C_9H_{13}ON,C_6H_3O_7N_3$ requires C, 47·4; H, 4·2; N, 14·7%).

2 : 3-*Dihydro*-3-*keto*-4-*methylbenz*-1 : 4-*oxazine* (II).—To *N*-methyl-*o*-anisidine (120 g.) in dry benzene (700 c.c.) and pyridine (70 c.c.), freshly distilled chloroacetyl chloride (67·5 c.c.) in dry benzene (300 c.c.) was added slowly with shaking and cooling. The mixture was set aside overnight at room temperature and then heated under reflux for 1 hour at 100°. After cooling, the mixture was treated with water to dissolve precipitated salts, the separated benzene solution was washed with dilute hydrochloric acid and then with water until neutral, dried, and evaporated completely on the water-bath under reduced pressure. The residue (168 g.) was treated with powdered anhydrous aluminium chloride (130 g.) (temperature rise to 130°). Further aluminium chloride (130 g.) was added and the mixture heated, with constant stirring, to 150—160° (bath-temperature) until evolution of gases had diminished (1½ hours). The thick mixture was poured on a tile, allowed to cool, powdered, added, with stirring, to crushed ice (1 kg.), and set aside overnight at 0°. The supernatant liquor was decanted, with filtration, and the sticky brown product was stirred with 7·5% sodium hydroxide solution (750 c.c.) wherein a small proportion dissolved and the remainder gradually became granular. The insoluble material (80 g.) was dissolved in ether, shaken with dilute sodium hydroxide solution, filtered, and washed with water until neutral. After drying and removal of the solvent, the residue was distilled, giving a pale yellowish solid, b. p. 127—129°/3 mm., with a faint, camphor-like odour. This crystallised from light petroleum (b. p. 60—80°), containing a little benzene, as colourless rods, m. p. 57—58° (Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 2188, give m. p. 58—59° for this benzoxazine derivative) (Found: C, 66·4; H, 5·4; N, 8·4; *N*-Me, 8·5. Calc. for $C_9H_9O_2N$: C, 66·3; H, 5·5; N, 8·6; *N*-Me, 9·2%).

Rearrangement of 2 : 3-*Dihydro*-3-*keto*-4-*methylbenz*-1 : 4-*oxazine*.—Powdered anhydrous aluminium chloride (63·5 g.) was stirred into the molten benzoxazine derivative (31 g.), and the mixture heated (oil-bath) with constant stirring. At 215°, reaction set in and the temperature rose spontaneously to 225°, acid vapours being evolved. Heating at 220° was continued for 1 hour after which the thick brown paste was removed, allowed to cool, powdered, and decomposed by addition to crushed ice (200 g.). Concentrated hydrochloric acid (30 c.c.) was added, and the mixture set aside overnight at 0°. The solid product was then filtered off and washed with cold water, and the acidic material was dissolved in dilute aqueous sodium hydroxide. From the alkaline solution ether removed unchanged 2 : 3-dihydro-3-keto-4-methylbenz-1 : 4-oxazine (6·7 g.). The aqueous solution was filtered and acidified with concentrated hydrochloric acid. After 3 hours at 0° the precipitated pale brown solid was filtered off, washed with water, and dried (20 g.).

The crude product (19 g.), dissolved in 7·5% sodium hydroxide solution (68 c.c.), was shaken during the gradual addition of neutral methyl sulphate (13·5 c.c.). An oil separated. The reaction was completed on the water-bath (30 minutes), with small additions of sodium hydroxide solution to maintain alkalinity. Next morning, the mixture was neutralised and extracted with ethyl acetate (500 c.c.). The extract was washed with cold water, the solvent removed under reduced pressure on the water-bath, and the residue distilled. The pale yellowish, solid distillate, b. p. 118—123°/0·25 mm. (11·5 g.), was extracted with several portions of cold ether. The undissolved residue formed colourless, stout prisms (4·0 g.) which, recrystallised from hot water, yielded glistening needles or leaflets, m. p. 137—138°, subsequently shown to be 4-*methoxy*-1-*methyloxindole* (Found: C, 67·9; H, 6·0; N, 7·85; OMe, 16·8; *N*-Me, 7·9. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9; OMe, 17·5; *N*-Me, 8·5%). The combined ethereal washings were concentrated by evaporation at room temperature. A further crop, of m. p. 137° (0·3 g.), was obtained, but the remainder of the solute (*ca.* 7·0 g.) consisted of a second product which crystallised from the mother-liquor in well-defined clusters of flat, yellowish needles. These crystals were recrystallised from ether, purified in ether on alumina, and again recrystallised from ether, yielding 7-*methoxy*-1-*methyloxindole* (VI; R = Me) (see below) as long, pointed, colourless leaflets, m. p. 101—102° (Found: C, 67·7; H, 6·2; N, 7·8; OMe, 16·7, 16·9, 17·3; *N*-Me, 7·0, 6·6. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9; OMe, 17·5; *N*-Me, 8·5%).

The experiment was repeated with similar results on specially purified 2 : 3-dihydro-3-keto-4-methylbenz-1 : 4-oxazine, but neither the 2-methyl nor the methyl-free parent compound yielded appreciable quantities of hydroxyindoles on treatment with excess of aluminium chloride at 220—250° for periods up to 1 hour.

2 : 3-*Dihydro*-3-*keto*-2-*methylbenz*-1 : 4-*oxazine*.—α-Bromopropionyl-*o*-anisidide was heated with aluminium chloride to 160° for 15 minutes and the cooled mixture was decomposed with crushed ice. An almost colourless, lachrymatory solid—probably the α-bromopropionyl-*o*-hydroxyanilide—separated and readily dissolved in dilute aqueous sodium hydroxide. The alkaline solution rapidly deposited crystalline 2 : 3-dihydro-3-keto-2-methylbenz-1 : 4-oxazine which formed colourless needles, m. p. 144·5—145·5°, from aqueous ethanol (Bischoff, *Ber.*, 1900, **33**, 1593, gives m. p. 144—145°) (Found : C, 66·4; H, 5·25; N, 8·6. Calc. for $C_9H_9O_2N$: C, 66·3; H, 5·5; N, 8·6%).

2 : 3-*Dihydro*-3-*ketobenz*-1 : 4-*oxazine*.—Chloroacetyl-*o*-anisidide, heated with four times its weight of aluminium chloride to 175—190° for 1 hour, yielded 2 : 3-dihydro-3-keto-1 : 4-oxazine after decomposition of the cooled reaction mixture with ice, filtration, and treatment with dilute aqueous sodium hydroxide. The product formed colourless leaflets, m. p. 172—173°, from aqueous ethanol (2 : 1) (Jacobs and Heidelberger, *loc. cit.*, give m. p. 173°) (Found : C, 64·3; H, 4·4; N, 9·1. Calc. for $C_8H_7O_2N$: C, 64·4; H, 4·7; N, 9·4%).

7-*Methoxy*-1-*methylisatin*.—Oxalyl chloride (26 g.) in dry benzene (75 c.c.) was mixed with *N*-methyl-*o*-anisidine (13 g.) in dry benzene (25 c.c.), and the clear yellow solution was refluxed for 3 hours. The solvent was then removed under reduced pressure on the water-bath and the oily residue was treated in dry ethylene dichloride (100 c.c.) with powdered aluminium chloride (13 g.), in small portions, with cooling. The dark red mixture was set aside for 25 hours with occasional shaking at room temperature, then poured on ice (250 g.). The organic layer was washed successively with 0·1N-hydrochloric acid (3 × 20 c.c.), water, and dilute aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated on the water-bath under reduced pressure. The semi-solid residue (15 g.) was boiled with aqueous ethanol (charcoal); after filtration and cooling, dark red crystals separated (2 g.) and were filtered off. Dilution of the mother-liquor with water caused the precipitation of a red oil which was not investigated. Recrystallisation of the solid from ethanol yielded blood-red needles of 7-methoxy-1-methylisatin, m. p. 186·5—187° (Kaufmann and Rothlin, *Ber.*, 1916, **49**, 578, give m. p. 187°) (Found : C, 62·7; H, 4·8; N, 7·5. Calc. for $C_{10}H_9O_3N$: C, 62·8; H, 4·7; N, 7·3%). An attempt to reduce the isatin by lithium aluminium hydride in ether afforded only a small quantity of a steam-volatile indole and an unidentified, non-volatile material which on passage in ether through alumina changed from green to deep blue and gave tiny purple prisms of m. p. 208—210°.

7-*Methoxy*-1-*methylisatin* β-*Oxime*.—(*a*) 7-Methoxy-1-methylisatin (65 mg.) was heated with hydroxylamine hydrochloride (30 mg.) and crystallised sodium acetate (50 mg.) in water (2 c.c.) on the steam-bath for 1 hour, after which the isatin crystals had been replaced by yellow crystals of the *oxime*. The mixture was cooled and the very sparingly soluble solid filtered off. It separated from water–ethanol (2 : 1) in fine, golden-yellow needles, m. p. 234—235° (decomp.), softening at 225° when the temperature was raised at a rate not greater than 3°/minute. The m. p. varied slightly with the rate of heating (Found : C, 55·2; H, 5·15; N, 12·9; OMe, 14·1; *N*-Me, 3·2. $C_{10}H_{10}O_3N,\frac{1}{2}H_2O$ requires C, 55·8; H, 5·1; N, 13·0; OMe, 14·4; *N*-Me, 6·9%).

(*b*) 7-Methoxy-1-methyloxindole (25 mg., prepared *via* 2 : 3-dihydro-3-keto-4-methylbenz-1 : 4-oxazine) in glacial acetic acid (1 c.c.) was treated with a few drops of concentrated aqueous sodium nitrite. The solution became yellow and was set aside for 1 hour. Dilution with water (6 c.c.) afforded a fine crystalline solid, which was filtered off, washed with water, and crystallised from water–ethanol (2 : 1) as golden-yellow needles, m. p. 230—231° (decomp.), softening at 220°, and m. p. 232—233° (decomp.) on admixture with 7-methoxy-1-methylisatin oxime (above). When 4-methoxy-1-methyloxindole was treated with nitrous acid in glacial acetic acid as described for 7-methoxy-1-methyloxindole, little or no reaction occurred, a good yield of starting material being recovered.

7-*Methoxy*-1-*methyldioxindole*.—Sodium hydrosulphite (dithionite) (0·51 g.) was added in small portions to a gently boiling suspension of 7-methoxy-1-methylisatin (0·39 g.) in water (10 c.c.) (cf. Marschalk, *Ber.*, 1912, **45**, 583). The red crystals of the isatin were rapidly replaced by a colourless solid which dissolved when more water (5 c.c.) was added and boiling continued. After concentration to 5 c.c., the solution was cooled and set aside in a stoppered vessel for 2 hours at 0°. The product, a pale pink solid (0·275 g.), was filtered off and washed with ice-water, and after crystallisation from hot water containing a trace of sodium hydrosulphite formed colourless prisms of 7-*methoxy*-1-*methyldioxindole* which became brown at 150° and melted with decomposition at 170—175° after softening at 160° (Found : C, 61·9; H, 5·3; N, 7·4. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·25%). The compound, in hot aqueous solution, was readily oxidised by air to the isatin.

7-*Methoxy*-1-*methyloxindole* (I).—7-Methoxy-1-methyldioxindole, suspended in dilute aqueous

ethanol, or in dilute acetic acid at 0°, was not readily reduced by 5% sodium amalgam at 0° during passage of carbon dioxide (cf. Marschalk, *loc. cit.*). The reduction was successful under the following conditions (cf. Baeyer and Knop, *Annalen*, 1865, **140**, 29). A solution of 7-methoxy-1-methyldioxindole (50 mg.) in boiling water (5 c.c.) was made weakly acid with dilute sulphuric acid and treated gradually with 5% sodium amalgam, with occasional additions of acid to maintain acidity, until the reddish colour was completely discharged (40 minutes). The hot mixture was then filtered and the filtrate on cooling deposited slender, colourless needles of 7-methoxy-1-methyloxindole, identical with the product, m. p. 101—102°, obtained by rearrangement of the benzoxazine derivative (Found: OMe, 16·5; *N*-Me, 5·1%).

2-Methoxy-6-nitrobenzyl Cyanide (V; R = CN).—Crude 2-methoxy-6-nitrobenzyl chloride (4·5 g.) (Buehler, Deebel, and Evans, *J. Org. Chem.*, 1941, **6**, 217) in ethanol (4·5 c.c.) was heated under reflux with a solution of potassium cyanide (1·6 g.) in water (1·5 c.c.). After 6 hours the mixture was cooled and extracted with ether in which some dark brown resinous material did not dissolve. The ethereal solution was washed with water, dried, and concentrated, yielding a reddish oil which partly crystallised on being rubbed. *2-Methoxy-6-nitrobenzyl cyanide* crystallised from ethanol–water (1 : 1) (charcoal) as yellow, light-sensitive leaflets of m. p. 78—79° (Found: C, 56·4; H, 4·2; N, 14·3. $C_9H_8O_3N_2$ requires C, 56·25; H, 4·2; N, 14·6%).

2-Methoxy-6-nitrophenylacetic Acid (V; R = CO_2H).—The above nitrile (4·2 g.; crude) was refluxed with concentrated hydrochloric acid (125 c.c.) for 6 hours, after which a little tar remained undissolved. When the mixture was cooled crystals separated readily and after filtration were stirred and warmed with dilute aqueous sodium carbonate on the steam-bath for 10 minutes. Charcoal was added and stirring continued whilst the mixture cooled. After filtration the solution was acidified and, after an hour at 0°, the straw-coloured solid was filtered off (1·8 g.). *2-Methoxy-6-nitrophenylacetic acid* crystallised from hot water containing a little ethanol as very pale yellow prisms, m. p. 171—172° (Found: C, 51·45; H, 4·1; N, 7·2. $C_9H_9O_5N$ requires C, 51·2; H, 4·3; N, 6·7%).

4-Methoxyoxindole (VI; R = H).—Catalytic hydrogenation (palladium black) of 7-methoxy-6-nitrophenylacetic acid (0·5 g.) in glacial acetic acid (10 c.c.) at room temperature gave 4-methoxyoxindole (0·38 g.), recovered by distillation of the solvent on the water-bath under reduced pressure. The product, crystallised from ethanol–water (1 : 5), formed pale yellow needles, m. p. 196—197° (Found: C, 66·5; H, 5·8; N, 8·7. $C_9H_9O_2N$ requires C, 66·25; H, 5·5; N, 8·6%).

4-Methoxy-1-methyloxindole (VI; R = Me).—4-Methoxyoxindole (0·326 g.) was dissolved in absolute methanol (4 c.c.) containing sodium methoxide (from 0·046 g. of sodium), and the solution refluxed with methyl iodide (0·284 g.) at 40—45° for 6 hours. The solvent was then distilled from the dark brown solution and the residue, a brown oil, was treated while still warm with 10% aqueous sodium hydroxide (2 c.c.). Crystals immediately separated and, after cooling, were filtered off. They (0·067 g.) were washed with cold water and after recrystallisation from hot water containing a little ethanol formed leaflets or small pale yellow prisms, m. p. 136·5—137° unchanged on admixture with the compound of m. p. 137—138° obtained *via* the benzoxazine derivative.

7-Methoxy-1-methylindole.—(*a*) Reduction of 7-methoxy-1-methyloxindole with lithium aluminium hydride as described for the 4-methoxy-isomer yielded *7-methoxy-1-methylindole* which, after purification in light petroleum (b. p. 60—80°) on alumina, formed lustrous colourless leaflets, m. p. 54·5—55·5°, from that solvent (Found: C, 74·6; H, 6·8; OMe, 18·45; *N*-Me, nil. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; OMe, 19·25; *N*-Me, 9·3%). The *picrate* formed chocolate-brown needles, m. p. 151°, from ethanol (Found: C, 49·5; H, 3·5. $C_{10}H_{11}ON,C_6H_3O_7N_3$ requires C, 49·2; H, 3·6%). From the acid washings of the reduction product a small quantity of oily 7-methoxy-1-methylindoline was recovered and was characterised as the *picrate*, yellow prisms, softening at 130°, m. p. 145—148° (uncorrected) (from ethanol) (Found: C, 49·2; H, 4·1; N, 13·9, 14·2; OMe, 7·8; *N*-Me, nil. $C_{10}H_{13}ON,C_6H_3O_7N_3$ requires C, 49·0; H, 4·1; N, 14·3; OMe, 7·9; *N*-Me, 3·8%).

(*b*) To a solution of potassium (60 mg.) in liquid ammonia (5 c.c.) containing a small crystal of ferric nitrate was added, dropwise and with stirring, 7-methoxyindole (212 mg.) in dry ether (1 c.c.), and then methyl iodide (0·092 c.c.) also in dry ether (1 c.c.). After 30 minutes the solvents were evaporated and the recovered solid (202 mg.) was purified in light petroleum (b. p. 60—80°) on alumina. The product was obtained as colourless leaflets, m. p. 54—54·5°, from light petroleum (b. p. 60—80°), the m. p. being slightly raised by admixture with the indole prepared as in (*a*) (Found: OMe, 18·4; *N*-Me, nil). The picrate had m. p. and mixed m. p. with the sample from (*a*) 151°.

4-Methoxy-1-methylindole (VII; R = H).—Finely powdered 4-methoxy-1-methyloxindole

(5 g.), suspended in dry ether (100 c.c.), was treated, with stirring and exclusion of moisture, with powdered lithium aluminium hydride (0·8 g.) in small portions during 20 minutes. The mixture was stirred for a further 20 minutes; then water (25 c.c.) was slowly added, followed by N-hydrochloric acid (50 c.c.). After being thoroughly shaken, the solvent layers were separated and the ethereal solution was washed with N-hydrochloric acid (2 × 25 c.c.). The green ethereal solution was dried (K_2CO_3) and evaporated, and the residue distilled in steam. When the distillation was concluded, unreduced 4-methoxy-1-methyloxindole, which was not appreciably volatile in steam, was recovered on cooling as a crystalline solid (0·5 g.). The distillate was extracted with ether from which *4-methoxy-1-methylindole* (3 g.) was recovered. It crystallised from light petroleum (b. p. 60—80°) containing a little ethanol as colourless, flattened prisms, m. p. 89° (Found: C, 74·4; H, 6·8; N, 8·5; OMe, 18·7; *N*-Me, 8·6. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·7; OMe, 19·25; *N*-Me, 9·3%). The *picrate* crystallised as dark red needles (from ethanol), m. p. 153° (Found: 49·3; H, 3·9; N, 14·2. $C_{10}H_{11}ON,C_6H_3O_7N_3$ requires C, 49·2; H, 3·6; N, 14·4%). The acid washings from the reduction were made alkaline and extracted with ether. After washing and removal of the ether, 4-methoxy-1-methylindoline (0·72 g.) was distilled as a very pale yellow oil, b. p. (bath-temperature) 95—97° (uncorr.)/10·5 mm., which yielded a *picrate* as yellow crystals (from ethanol), m. p. 163—164° (decomp.), softening at 157° (bath pre-heated to 150°) (Found: C, 48·8; H, 4·4; N, 14·2; OMe, 7·9; *N*-Me, 3·1. $C_{10}H_{13}ON,C_6H_3O_7N$ requires C, 49·0; H, 4·1; N, 14·3; OMe, 7·9; *N*-Me, 3·8%).

7-Methoxy-2-methylindole.—*o*-Methoxyphenylhydrazine (20 g.) was dissolved in glacial acetic acid (20 c.c.) and the mixture diluted with water (30 c.c.). When acetone (11 c.c.) was added to the slightly turbid solution heat was evolved and an oil separated rapidly. After being kept overnight at 0° the mixture was extracted with ether from which the hydrazone was recovered by evaporation on the warm water-bath under reduced pressure. The hydrazone (19 g.) was treated with powdered, anhydrous zinc chloride (19 g.), with good stirring, and the mixture then slowly heated to 110—120°/15 mm. under a reflux air-condenser. After 15 minutes a brief vigorous reaction commenced. Heating at 115° was continued for a further 30 minutes. The cooled mixture was dissolved in boiling, very dilute hydrochloric acid, and distilled in steam. A colourless oil, which gave strongly positive Ehrlich and vanillin reactions, distilled readily and quickly solidified. Periodically a hard cake which formed in the distillation flask was dissolved in a small quantity of ethanol and diluted with an equal volume of hot water, before resumption of the steam-distillation. The distillate was extracted with ether and the recovered *7-methoxy-2-methylindole* (1·53 g.) was purified in light petroleum (b. p. 60—80°) on alumina; from this solvent it crystallised as flat, colourless needles, m. p. 83—83·5°. It showed a tendency to become yellowish in air or in ether (Found: C, 74·7; H, 6·7; N, 8·5. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·7%). The *picrate* formed shining, brownish-red needles, m. p. 157—158°, from ethanol (Found: C, 49·5; H, 3·6; N, 14·0. $C_{10}H_{11}ON,C_6H_3O_7N_3$ requires C, 49·2; H, 3·6; N, 14·4%).

7-Methoxy-3-methylindole.—*o*-Methoxyphenylhydrazine (20 g.) was mixed with freshly distilled propaldehyde (15 c.c.) with shaking and cooling. Heat was evolved and the oily hydrazone separated rapidly. After being washed with cold water it was dissolved in a mixture of sulphuric acid (4 c.c.) and ethanol (50 c.c.). The solution immediately became hot and ammonium sulphate separated. The reaction was completed on the water-bath (30 minutes) after which the mixture was cooled, diluted with water (150 c.c.), and extracted with ether. The blue-fluorescent ethereal solution was washed and separated from some insoluble, sticky residue, and after drying (Na_2SO_4) the solvent was removed and the residue of dark oil was distilled in steam. A small quantity (0·5 c.c.) of anisole (b. p. 153°) was isolated from the first fraction of the distillate but the skatole was only sparingly volatile in steam. Accordingly, the undistilled residue was redissolved in ether, dried, and distilled after removal of the solvent. 7-Methoxy-3-methylindole distilled as a pale yellow oil, b. p. 150° (uncorr.)/15 mm. (5—6 g.) (Blaikie and Perkin, *J.*, 1924, **125**, 330, give b. p. 170°/20 mm.), and gave a picrate which crystallised as dark red needles, m. p. 158·5—159°, from ethanol (Blaikie and Perkin, *loc. cit.*, give m. p. 156°) (Found: C, 49·4; H, 3·9; N, 14·2. Calc. for $C_{10}H_{11}ON,C_6H_3O_7N_3$: C, 49·2; H, 3·6; N, 14·4%). The undistilled residue (*ca.* 4 c.c.), a very thick reddish transparent gum, was not investigated.

3-Dimethylaminomethyl-4-methoxy-1-methylindole (*4-Methoxy-1-methylgramine*) (VII; R = $CH_2{\cdot}NMe_2$).—Acetic acid (1 c.c.) was added to aqueous dimethylamine (33%; 1·05 c.c.), cooled in a freezing mixture so that the temperature did not exceed 5°. Aqueous formaldehyde (37%; 0·47 c.c.) was added and the mixture was quickly poured, with shaking, into finely powdered 7-methoxy-1-methylindole (1·07 g.). The mixture became warm and was shaken,

with occasional gentle warming to 40°, for 3 hours and then left at room temperature for 24 hours. The pale-brown mixture was poured into 10% aqueous sodium hydroxide (20 c.c.) and after 3 hours at 0° a yellow-brown gum was collected and treated with N-hydrochloric acid (20 c.c.) and ether (10 c.c.). After being freed from some insoluble material the solvent layers were separated and the aqueous layer was washed with ether and made alkaline at 0°. 4-Methoxy-1-methylgramine, recovered in ether, was an oil (1·1 g.) which solidified on being rubbed at 0° but re-melted at room temperature. The *picrate* formed yellow prisms, m. p. 160—161°, from methanol (Found, after drying *in vacuo* over phosphoric oxide: C, 50·8; H, 4·4; N, 15·7. $C_{13}H_{18}ON_2,C_6H_3O_7N_3$ requires C, 51·0; H, 4·7; N, 15·7%). The *methiodide*, formed from its components in ethanol, crystallised as colourless leaflets from benzene–ethanol but was highly sensitive to atmospheric moisture [Found: (1st specimen) C, 39·9, 40·2; H, 5·3, 6·2: (2nd specimen) C, 41·6; H, 5·9. $C_{14}H_{21}ON_2I,3H_2O$ requires C, 40·6; H, 6·5%].

Ethyl α-Acetamido-α-carbethoxy-β-(4-methoxy-1-methyl-3-indolyl)propionate [VII; R = $CH_2{\cdot}C(NHAc)(CO_2Et)_2$].—4-Methoxy-1-methylgramine methiodide (1·72 g.) was added to a solution of ethyl acetamidomalonate (1·04 g.) in ethanol (11 c.c.) containing sodium ethoxide (from 0·11 g. of sodium), and the mixture was heated under reflux for 24 hours by which time evolution of trimethylamine had practically ceased. The filtered solution was poured into cold water (100 c.c.). The gum obtained rapidly solidified (1·35 g.). It was purified for analysis by passage in benzene through a column of alumina, the recovered *ester* being obtained as colourless prisms, m. p. 144—145°, from benzene–light petroleum (b. p. 60—80°) (1 : 2) (Found: C, 61·7; H, 6·5; N, 7·4. $C_{20}H_{26}O_6N_2$ requires C, 61·5; H, 6·7; N, 7·2%).

α-Acetamido-β-(4-methoxy-1-methyl-3-indolyl)propionic Acid [VII; R = $CH_2{\cdot}CH(NHAc){\cdot}CO_2H$].—The foregoing ester (1·25 g.) was heated under reflux with a solution of sodium carbonate (1·25 g.) in water (12·5 c.c.) for 22 hours after which time only a small quantity of a dark oil remained undissolved. This was removed in ether. Acidification of the carbonate solution afforded the *acid* (0·73 g.) as long pointed leaflets (from ethanol–water, 1 : 2) which when slowly heated softened slightly at 120° and melted at 190—195° but when rapidly heated melted with effervescence at 120—125° (Found: C, 58·35; H, 6·3; N, 9·2. $C_{15}H_{18}O_4N_2,H_2O$ requires C, 58·4; H, 6·5; N, 9·1%).

α-Amino-β-(4-methoxy-1-methyl-3-indolyl)propionic Acid (*4-Methoxy-1-methyltryptophan*).—The foregoing acetyl derivative (0·63 g.) was heated with water (10 c.c.) at 180—190° for 6 hours. The *tryptophan*, recovered from the concentrated solution (charcoal), formed nearly colourless, flat needles, m. p. *ca.* 250° (decomp.), from ethanol–water (1 : 1) (Found: C, 62·7; H, 6·7; N, 11·0. $C_{13}H_{16}O_3N_2$ requires C, 62·9; H, 6·45; N, 11·3%).

2 : 3 : 4 : 5-Tetrahydro-6-methoxy-1 : 2-dimethyl-β-carboline-4-carboxylic Acid (VIII).—A solution of 4-methoxy-1-methyltryptophan (0·35 g.) in hot water (50 c.c.) was rapidly cooled and treated with freshly distilled acetaldehyde (1 c.c.). After 24 hours at room temperature, during which a slight deposition occurred, the mixture was warmed at 50—70° in a stoppered flask for 12 hours and then left at room temperature overnight. The mixture was evaporated to dryness on the water-bath affording a solid residue (0·38 g.) which gave only a weakly positive ninhydrin reaction, and yielded the *tetrahydrocarbolinecarboxylic acid* as tiny, cream-coloured leaflets, softening at 250°, m. p. 255—257° (decomp.), from hot water (charcoal) (Found: C, 61·6; H, 6·4; N, 9·8. $C_{15}H_{18}O_2N_2,H_2O$ requires C, 61·6; H, 6·8; N, 9·6%).

6-Methoxy-1 : 2-dimethyl-β-carboline (IX) was prepared by treating the foregoing acid (0·28 g.) in hot aqueous solution (170 c.c.) with 10% aqueous potassium dichromate (14 c.c.) and acetic acid (3 c.c.). The whole was boiled for 3 minutes, cooled, and treated with an excess of aqueous sodium sulphite and then with a saturated solution of sodium carbonate. The carboline (0·14 g.), recovered in ether and purified in benzene on alumina, formed very pale yellowish prisms, m. p. 139—140°, from benzene–light petroleum (b. p. 60—80°) (3 : 1) (Found: C, 74·4; H, 5·9; N, 12·15. Calc. for $C_{14}H_{14}O_4N_2$: C, 74·3; H, 6·2; N, 12·4%). The picrate formed masses of tiny yellow needles, m. p. *ca.* 267° (decomp.), from methanol (Found, after drying at 100°/15 mm. for 1 hour over phosphoric oxide: C, 52·9; H, 3·9. Calc. for $C_{14}H_{14}ON_2,C_6H_3O_7N_3$: C, 52·75; H, 3·7%). The *p*-nitrobenzylidene derivative was formed by heating the base (20 mg.) with *p*-nitrobenzaldehyde (100 mg.) at 250—255° for 5 minutes, cooling, extracting the product in benzene, and shaking the benzene solution with dilute hydrochloric acid whereupon the insoluble hydrochloride was formed and was decomposed by treatment with cold dilute aqueous sodium hydroxide. The base formed golden-yellow needles, m. p. 264°, from benzene (Found: C, 70·2; H, 4·9. Calc. for $C_{21}H_{17}O_3N_3$: C, 70·2; H, 4·7%).

The sample (5—8 mg.) of the degradation product of mitragynine, as supplied by Dr. Ing, had m. p. 129—134° (softening at 120°). It was passed in benzene through a column of alumina

and eluted with benzene. The recovered base yielded almost colourless crystals, m. p. 138·5—139·5° from (1 : 4) benzene–light petroleum (b. p. 60—80°). The following table summarises the m. p. and mixed m. p. behaviour of the degradation products (A) from mitragynine and the synthetic samples (B) of the 6-methoxy-1 : 2-dimethyl-β-carboline series :

	A	B	A + B
Base	m. p. 138·5—139·5°	m. p. 139—140°	m. p. 138·5—139·5°
Picrate	decomp. *ca.* 260°	decomp. *ca.* 267°	decomp. *ca.* 265°
p-Nitrobenzylidene derivative	m. p. 261°	m. p. 264°	m. p. 263°

We are greatly indebted to Dr. H. R. Ing, F.R.S., for placing at our disposal the carboline base obtained by degradation of mitragynine, and to this University for the award of a grant (to P. McC.). Microanalyses were carried out by Mr. J. M. L. Cameron and Miss M. W. Christie.

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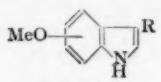
750. *The Chemistry of the* Mitragyna *Genus. Part IV.* Derivatives of Harman.*

By G. G. DOIG, J. D. LOUDON, and P. MCCLOSKEY.

Syntheses of 9-methoxy-, 9-methoxy-1-methyl-, and 6-methoxy-1-methyl-β-carboline complete the set of eight harman derivatives which contain a methoxyl group in the benzene nucleus, with or without a 1-methyl substituent. The ultra-violet absorption spectra of these eight compounds and of 1 : 2-dimethyl-β-carboline are recorded.

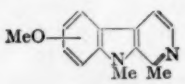
THE identification of 6-methoxy-1 : 2-dimethyl-β-carboline as a degradation product of mitragynine (Part III;* cf. Ing and Raison, *J.*, 1939, 986) adds to the growing list of harman derivatives which have a bearing on the chemistry of indole alkaloids (cf. T. A. Henry, " The Plant Alkaloids," Churchill, London, 1949). It was the object of the present work to complete and characterise as reference compounds those derivatives of harman and of *ind-N*-methylharman, which contain a methoxyl substituent in the benzene ring. Five of these compounds were already known (for references, see Experimental section): the remaining three have now been synthesised and the ultra-violet absorption spectra of the eight compounds are here recorded.

The same general procedure served for the preparation of all of the required compounds (cf. Part II; Cook, Loudon, and McCloskey, *J.*, 1951, 1203; Part III *). From the methoxyindole (I; R = H), the gramine (I; R = CH_2·NMe_2) and tryptophan [I; R = CH_2·$CH(NH_2)$·CO_2H], and thence, *via* the 2 : 3 : 4 : 5-tetrahydro-2-methylcarboline-4-carboxylic acid, the harman derivative (II) were produced. The methosulphate of (II) was converted into the anhydronium base and thence by addition of methyl iodide into the 1 : 2 : 3-trimethyl-β-carbolinium iodide which on pyrolysis yielded (III). 6-Methoxy-1 : 2-dimethyl-β-carboline, prepared in this way from 6-methoxyharman, was identical with the compound synthesised by the alternative route described in Part III, and 1 : 2-dimethyl-β-carboline (III; H for MeO) was similarly prepared from harman (II; H for OMe).



(I)

(II)



(III)

The ultra-violet absorption spectra of the four methoxyharmans and their 1-methyl derivatives are shown in Figs. 1—4. The spectrum of 1-methylharman is included (Fig. 1) and shows a general resemblance to the spectra of harman (Raymond-Hamet, *Compt. rend.*, 1945, **221**, 387) and 2-ethyl-β-carboline (Leonard and Elderfield, *J. Org. Chem.*, 1942, **7**, 556). Similar resemblances are found in the absorption curves of the methoxylated harmans when compared respectively with those of their 1-methyl derivatives. The

* Part III, preceding paper.

position of the methoxyl group in the benzene ring has considerable influence on the absorption. The curves of the 6- and the 9-methoxy-compound, with α-methoxy-groups (Figs. 2 and 4), resemble each other, but those of the 7- and the 8-methoxy-compound (Figs. 1 and 3), with β-methoxy-groups, show appreciable differences. We are indebted

FIG. 1.

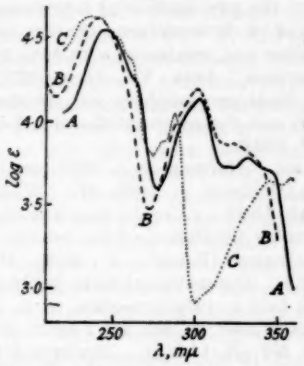


FIG. 2.

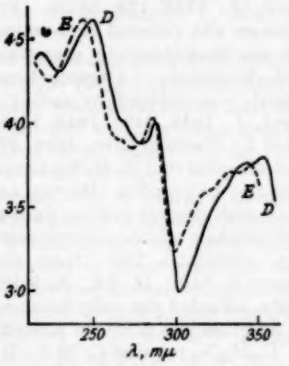


FIG. 1. *A*, 8-*Methoxy*-1 : 2-*dimethyl*-β-*carboline*, *max. at* 245, 303, *and* 332 mμ, log ε 4·55, 4·15, *and* 3·79.
B, 8-*Methoxy*-2-*methyl*-β-*carboline*, *max. at* 242 *and* 301 mμ, log ε 4·62 *and* 4·20.
C, 1 : 2-*Dimethyl*-β-*carboline*, *max. at* 237, 288, 346, *and* 359 mμ, log ε 4·63, 4·05, 3·65 *and* 3·67.

FIG. 2. *D*, 6-*Methoxy*-1 : 2-*dimethyl*-β-*carboline*, *max. at* 218, 249, 288, 342, *and* 352 mμ, log ε 4·42, 4·62, 4·01, 3·76, *and* 3·80.
E, 6-*Methoxy*-2-*methyl*-β-*carboline*, *max. at* 244, 286, 333, *and* 344 mμ, log ε 4·62, 4·03, 3·72, *and* 3·74.

FIG. 3.

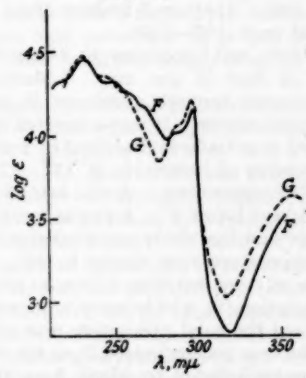


FIG. 4.

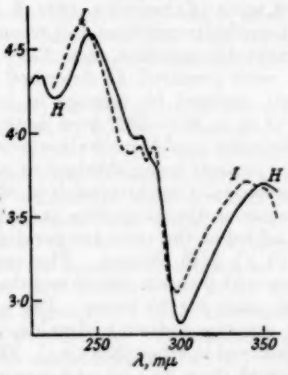


FIG. 3. *F*, 7-*Methoxy*-1 : 2-*dimethyl*-β-*carboline*, *max. at* 231 *and* 298 mμ, log ε 4·46 *and* 4·16.
G, 7-*Methoxy*-2-*methyl*-β-*carboline*, *max. at* 231, 296, *and* 358 mμ, log ε 4·48, 4·21, *and* 3·64.

FIG. 4. *H*, 9-*Methoxy*-1 : 2-*dimethyl*-β-*carboline*, *max. at* 213, 218, 247, 278, *and* 350 mμ, log ε 4·34, 4·35, 4·59, 3·98 ,*and* 3·69.
I, 9-*Methoxy*-2-*methyl*-β-*carboline*, *max. at* 242, 276, 284, *and* 340 mμ, log ε 4·66, 3·92, 3·91, *and* 3·70.

All spectra are for ethanol solutions.

to Dr. W. F. Short for a specimen of harmine from the collection of the late Dr. F. L. Pyman, F.R.S. For absorption measurements this specimen was purified by passing a solution in benzene through alumina, followed by recrystallisation. The absorption curve (Fig. 1) shows lower maximal intensities and a more pronounced flattening in the region, 320—340 mμ, than does the curve of " Harmin reinst " as given by Pruckner and Witkop (*Annalen*, 1943, **554**, 136).

Experimental.

4- and 7-Methoxyindole which were required for the synthetic work were prepared essentially as described by Blaikie and Perkin (*J.*, 1924, **125**, 296) from 6-methoxy- and 3-methoxy-2-nitrotoluene respectively, and these were obtained by methylating the corresponding nitrocresols with methyl sulphate and alkali. 3-Hydroxy-2-nitrotoluene was prepared by Haworth and Lapworth's method (*J.*, 1923, **123**, 2993). For the preparation of 6-hydroxy-2-nitrotoluene, 2 : 4 : 6-trinitrotoluene was reduced to 4-amino-2 : 6-dinitrotoluene (Parkes and Farthing, *J.*, 1948, 1275) which was deaminated by diazotisation and treatment with 30% hypophosphorous acid (method: cf. Kornblum, "Organic Reactions," 1944, Vol. II, p. 277). 2 : 6-Dinitrotoluene, so obtained, was reduced by sodium hydrogen sulphide (cf. standard procedure of Hodgson and Ward, *J.*, 1948, 242; 1949, 1316) and the resultant 6-amino-2-nitrotoluene was treated as described by Noelting (*Ber.*, 1904, **37**, 1024).

1 : 2-*Dimethyl*-β-*carboline* (ind-N-*Methylharman*).—Harman, m. p. 238° (corr.) (from benzene), was prepared from (±)-tryptophan (Harvey and Robson, *J.*, 1938, 97). When it (0·2 g.) was heated under reflux with neutral methyl sulphate (0·25 c.c.) in dry benzene (6 c.c.) for 1 hour, it formed the *methosulphate* which was recovered by distillation of the solvent and crystallised as needles, m. p. (decomp.) 262°, from methanol (Found: C, 54·6; H, 5·3; N, 9·0. $C_{14}H_{16}O_4N_2S$ requires C, 54·5; H, 5·2; N, 9·1%). The methosulphate (0·246 g.), treated with N-sodium hydroxide, afforded the anhydronium *base* as yellow needles, m. p. (decomp.) 177—178°, from water, and this was dried for analysis at 140°/20 mm. for 2 hours (Found: C, 79·0; H, 6·5; N, 14·2. $C_{13}H_{12}N_2$ requires C, 79·5; H, 6·2; N, 14·3%). The base (0·1 g.) and methyl iodide were mixed, and after 18 hours at room temperature were gently heated for 30 minutes and afforded, after evaporation, 1 : 2 : 3-*trimethyl*-3-*carbolinium iodide* as yellow clusters of needles which softened at 270° and melted at 279—281° (Found: C, 49·5; H, 4·3; N, 8·3. $C_{14}H_{15}N_2I$ requires C, 49·7; H, 4·5; N, 8·3%). This salt was heated in a sublimation tube at 290°/0·5 mm. for 1 hour. The sublimate was resublimed and gave *ind*-*N*-methylharman as colourless platelets, m. p. 102°, from light petroleum (b. p. 60—80°) (Found: C, 79·5; H, 6·3; N, 14·4. Calc. for $C_{13}H_{12}N_2$: C, 79·6; H, 6·2; N, 14·3%). Mukherji, Robinson, and Schlittler record m. p. 102° for *ind*-*N*-methylharman prepared from harmân, potassamide, and methyl iodide in liquid ammonia (*Experientia*, 1949, **5**, 215); Späth and Lederer (*Ber.*, 1930, **63**, 2102) prepared it from 1-methyltryptamine and record m. p. 102—103°.

7-Methoxy-2-methyl-β-carboline, m. p. 275—276°, and 7-methoxy-1 : 2-dimethyl-β-carboline, m. p. 130—131°, were prepared as described in Part II (*loc. cit.*). 8-Methoxy-2-methyl-β-carboline (harmine), purified by passage in benzene through a column of alumina, formed colourless needles of m. p. 261—262° from methanol–water. It was converted into 8-methoxy-1 : 2-dimethyl-β-carboline (*ind*-*N*-methylharmine) essentially as described by Iyer and Robinson (*J.*, 1934, 1935), the product being obtained as needles of (micro-)m. p. 122—123° (anhydrous).

3-*Dimethylaminomethyl*-4-*methoxyindole* (4-*Methoxygramine*).—Acetic acid (3 c.c.) was added dropwise to 25% aqueous dimethylamine (4 c.c.) kept below 5°. Aqueous formaldehyde (40%; 1·5 c.c.) was then added at the same temperature and the whole was poured into finely ground 4-methoxyindole (3 g.) with stirring. The temperature rose slowly to 25°; the suspended indole became pasty and then emulsified and the mixture was then shaken at room temperature for 1 hour and set aside for 20 hours. The solution, in which some solid was present, was basified with 10% aqueous sodium hydroxide, and the solid precipitate was collected, washed with water, and dissolved in ether (250 c.c.). The base was recovered from the ethereal solution in N-hydrochloric acid (3 × 20 c.c.) and was reprecipitated by alkali from the filtered acid solution. 4-*Methoxygramine* formed prisms, m. p. 142—143°, from benzene (charcoal) and then from ethanol–light petroleum (b. p. 60—80°) (Found: C, 70·6; H, 7·9; N, 14·0. $C_{12}H_{16}ON_2$ requires C, 70·6; H, 7·8; N, 13·7%).

Ethyl α-*Acetamido*-α-*carbethoxy*-β-(4-*methoxy*-3-*indolyl*)*propionate*.—Ethyl acetamidomalonate (5·94 g.) was added with stirring and exclusion of moisture to a cold solution of sodium methoxide (from 0·55 g of sodium) in dry ethanol (62 c.c.). 4-Methoxygramine (5·5 g.) was added and the whole was then treated dropwise with methyl sulphate (4·45 c.c.) under continuous stirring. After 16 hours at room temperature the reaction mixture was poured into water (200 c.c.), and the resultant solid precipitate was dissolved in chloroform and washed with N-hydrochloric acid (3 × 30 c.c.) and then with water. The *ester*, recovered from the dried chloroform solution, was obtained from ethanol as leaflets, which softened at 158° and melted at 162—163° (Found: C, 60·4; H, 6·4; N, 7·7. $C_{19}H_{24}O_6N_2$ requires C, 60·6; H, 6·4; N, 7·45%).

α-*Amino*-β-(4-*methoxy*-3-*indolyl*)*propionic Acid* (4-*Methoxytryptophan*).—The foregoing ester (10 g.) was heated under reflux with an aqueous solution (100 c.c.) of sodium carbonate (10 g.) for 18 hours. After filtration and extraction with ether the aqueous layer was acidified and the crude gummy acetamido-acid was collected. It (5·6 g.) was heated in a sealed tube with water (90 c.c.) at 180° for 6 hours, affording a solution which was treated with charcoal, filtered, and concentrated. 4-*Methoxytryptophan* was thereby obtained as prisms, darkening at 230° and m. p. (decomp.) 235—246°, from ethanol–water (1 : 3) (Found : C, 61·4; H, 6·0; N, 11·8. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0; N, 12·0%).

2 : 3 : 4 : 5-*Tetrahydro*-6-*methoxy*-2-*methyl*-β-*carboline*-4-*carboxylic Acid*.—Acetaldehyde (4 c.c.) was added to a cooled solution of 4-methoxytryptophan (1·6 g.) in water (240 c.c.) and after 24 hours at room temperature the solution was gradually heated and finally kept at 100° for 1 hour. The solution was decolorised by heating it with charcoal and, on concentration, afforded the *carboline acid*, m. p. 259—260° (with gas evolution) (from water) (Found : C, 60·2; H, 6·4; N, 10·3. $C_{14}H_{16}O_3N_2.H_2O$ requires C, 60·4; H, 6·5; N, 10·1%).

6-*Methoxy*-2-*methyl*-β-*carboline* (6-*Methoxyharman*).—To a solution of the foregoing acid (1·2 g.) in boiling water (500 c.c.) were added 10% aqueous potassium dichromate followed by acetic acid (12 c.c.). The whole was boiled for 3 minutes and the cooled mixture, in which a yellow solid had separated, was treated with an excess of aqueous sodium sulphate and then with a saturated solution of sodium carbonate. 6-*Methoxyharman* was recovered in ether and, after purification in chloroform on a column of alumina, formed almost colourless rods of m. p. (decomp.) 246—247° from chloroform–light petroleum (b. p. 60—80°) (Found : C, 73·3; H, 5·4; N, 13·4. $C_{12}H_{12}ON_2$ requires C, 73·6; H, 5·7; N, 13·2%).

6-*Methoxy*-1 : 2-*dimethyl*-β-*carboline*.—Following the procedure described for 1 : 2-dimethyl-β-carboline (above), 6-methoxyharman was converted into the *methosulphate*, pale yellow needles which softened at 272°, m. p. 285° (decomp.) (from methanol) (Found : C, 53·5; H, 5·4; N, 8·1. $C_{15}H_{18}O_5N_2S$ requires C, 53·4; H, 5·35; N, 8·3%), and thence into the corresponding base which was obtained as prisms, m. p. 234° (decomp.) from water but was not analysed. By reaction with methyl iodide the base afforded 6-*methoxy*-1 : 2 : 3-*trimethyl*-β-*carbolinium iodide* as brown-stained needles, m. p. 253—254° (decomp.), from aqueous ethanol (Found : C, 46·0, 46·2; H, 4·55, 4·45; N, 7·4. $C_{15}H_{17}ON_2I,H_2O$ requires C, 46·6; H, 4·9; N, 7·25%). Pyrolysis of this iodide gave 6-methoxy-1 : 2-dimethyl-β-carboline which, after sublimation and crystallisation from light petroleum (b. p. 60—80°), had m. p. 138° with softening at 135° and mixed m. p. 137—138° with the sample of m. p. 139—140° synthesised as described in Part III (*loc. cit.*).

9-*Methoxy*-2-*methyl*-β-*carboline* (9-*Methoxyharman*).—7-Methoxygramine, obtained as slender rods of m. p. 112·5° from ethanol–light petroleum (b. p. 60—80°) (Found : C, 70·25; H, 7·8; N, 13·7. Calc. for $C_{12}H_{16}ON_2$: C, 70·6; H, 7·8; N, 13·7%) (Bell and Lindwall, *J. Org. Chem.*, 1948, **13**, 547, give m. p. 105—106°), was prepared from 7-methoxyindole as described for the 4-methoxy-isomer and was similarly condensed with ethyl sodio-acetamidomalonate. *Ethyl* α-*acetamido*-α-*carbethoxy*-β-(7-*methoxy*-3-*indolyl*)*propionate* was thereby obtained as prisms, m. p. 147°, from ethanol (Found : C, 60·6; H, 6·5; N, 7·6. $C_{19}H_{24}O_6N_2$ requires C, 60·6; H, 6·4; N, 7·45%) and was hydrolysed in two stages (cf. 4-methoxy-isomer) to 7-methoxytryptophan, yellowish needles, m. p. (decomp.) about 250° (Found : C, 61·5; H, 5·7. Calc. for $C_{12}H_{14}O_3N_2$: C, 61·5; H, 6·0%) (Marchant and Harvey, *J.*, 1951, 1808, record m. p. 255—264° for an analytically impure specimen of the tryptophan). The reaction solution obtained by condensing 7-methoxytryptophan (4 g.) with acetaldehyde (10 c.c.) in water (600 c.c.) afforded on concentration (charcoal), as first and main fraction, needles (2·35 g.), m. p. 252—253°, and a residue, m. p. 230—244°, which appeared to contain unchanged metboxytryptophan, mixed m. p. 246—250°. Recrystallisation of the needles gave 2 : 3 : 4 : 5-tetrahydro-9-methoxy-2-methyl-β-carboline-4-carboxylic acid, m. p. (decomp.) 255—256°, from water, depressed to *ca.* 230—235° by admixture with the tryptophan (Found : C, 60·0; H, 6·6; N, 10·3. Calc. for $C_{14}H_{16}O_3N_2,H_2O$: C, 60·4; H, 6·5; N, 10·1%) (Marchant and Harvey, *loc. cit.*, give m. p. 256—258° for this monohydrate). Treatment of this carboline acid with potassium dichromate as described for the 6-methoxy-isomer gave 9-methoxyharman, m. p. 239—240°, from methanol (Späth and Lederer, *loc. cit.*, give the same m. p.)(Found : C, 73·6; H, 5·6; N, 13·3. Calc. for $C_{12}H_{12}ON_2$: C, 73·6; H, 5·7; N, 13·2%).

9-*Methoxy*-1 : 2-*dimethyl*-β-*carboline*.—As described for analogous cases, 9-methoxyharman was converted *via* the *methosulphate*, needles, m. p. 245° (from methanol) (Found : C, 53·15; H, 5·1; N, 8·1. $C_{15}H_{18}O_5N_2S$ requires C, 53·4; H, 5·35; N, 8·3%), and the corresponding base [needles, m. p. 167° (decomp.), from water] into 9-*methoxy*-1 : 2 : 3-*trimethyl*-β-*carbolinium*

iodide, needles, m. p. 294—295° (decomp.) (from much ethanol) (Found: C, 48·9; H, 4·7; N, 7·7. $C_{15}H_{17}ON_2I$ requires C, 48·9; H, 4·6; N, 7·6%). Pyrolysis of the iodide followed by resublimation of the product afforded *9-methoxy-1 : 2-dimethyl-β-carboline* as platelets, m. p. 164—165° [from light petroleum (b. p. 60—80°)] (Found: C, 74·45; H, 6·4; N, 12·5. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%. 7·175 Mg. of substance gave 14·37 mg. of silver iodide. Calc. for 1OMe and 1NMe group, 14·92 mg.).

We are indebted to the University of Glasgow for a research grant (to P. McC.) and to Imperial Chemical Industries Limited, Nobel Division, for a supply of 4-amino-2 : 6-dinitrotoluene. Grateful acknowledgment is also made to Professor J. W. Cook, F.R.S., for his interest and advice. Microanalyses were carried out by Mr. J. M. L. Cameron and Miss M. W. Christie.

UNIVERSITY OF GLASGOW. [*Received, May 17th*, 1952.]

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751. *The Vapour Pressure of the System Sulphuric Acid–Disulphuric Acid.*

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The vapour pressure of fuming sulphuric acid in the range of composition 50—63 moles % of sulphur trioxide (0—35% of " free " sulphur trioxide) has been determined at 20—80° by a static method. Where comparison is possible the measured pressures are usually lower than previously recorded values and reasons for this are discussed. The molar heat of evaporation of sulphur trioxide from the solution is in reasonably good agreement with thermal data. The measurements do not support the view that the oleums come into equilibrium slowly with respect to the components.

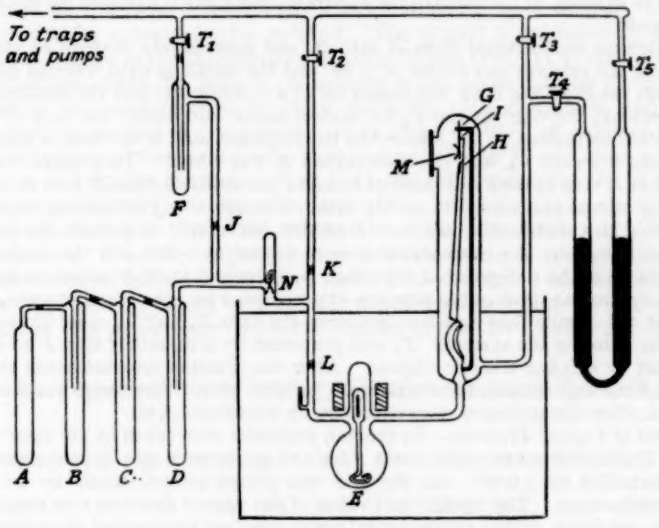
IN the course of experiments on the mechanism of aromatic sulphonation in fuming sulphuric acid (*J.*, 1950, 997, 1004) an attempt was made to evaluate the relative activity of the $HO{\cdot}SO_2^+$ cation in different media from the activity of sulphur trioxide and the H_0 function of the acid. Several determinations of the vapour pressure of fuming sulphuric acid have been published, but only a limited number of measurements referred to the required range of temperature and composition and the agreement between different authors left much to be desired. Re-determination of the vapour pressure of dilute oleums and application to the kinetics of aromatic sulphonation are discussed in this and the following paper.

Vapour-density determinations prove that sulphur trioxide vapour is unimolecular. The pure solid and the liquid phase, however, are complex aggregates of uni- and multimolecular forms of sulphur trioxide, and equilibrium between them is only established rapidly in the presence of traces of water. The anhydrous systems come into equilibrium very slowly and the physical properties show pronounced variations depending upon the history of the sample. Sulphur trioxide in dilute solution in sulphuric acid is present very largely as disulphuric acid, $H_2S_2O_7$ (this acid ionises slightly in the solution), but a small proportion exists in a free or physically solvated condition and is responsible for the vapour pressure. Apart from the low values of the vapour pressure, the conversion of the sulphur trioxide into disulphuric acid is demonstrated by Raman-spectral (Millen, *J.*, 1950, 2589) and freezing-point measurements (Gillespie, *J.*, 1950, 2493). It may be mentioned briefly that the vapour pressure is approximately proportional to the stoicheiometric molar ratio $H_2S_2O_7/H_2SO_4$ throughout a considerable range of composition, as shown (on a logarithmic scale) in Fig. 2B. Owing to the equilibrium $SO_3 + H_2SO_4 \rightleftharpoons H_2S_2O_7$, the pressure of sulphur trioxide is proportional to $([H_2S_2O_7]/[H_2SO_4]).f_{H_2S_2O_7}/f_{H_2SO_4}$, and it is, therefore, an experimental fact that this expression is very nearly proportional to the stoicheiometric ratio, moles $H_2S_2O_7/H_2SO_4$. This is readily understood if the equilibrium concentration

of free sulphur trioxide, compared with that of disulphuric acid, is small.* On the question of whether the uncombined sulphur trioxide in the solution is unimolecular or associated, however, there is no direct evidence.

The present measurements relate to moderately dilute oleums in the range of composition 50—63 moles % of sulphur trioxide (0—35% by weight of " free " sulphur trioxide). Workers in this field have reported widely different results and no wholly definitive reason for this can be given. It has been suggested that the fuming acids do not come to equilibrium rapidly and that the properties depend upon the pre-treatment or the method of preparation, but it is difficult to accept this hypothesis because traces of water (*i.e.*, sulphuric acid or polysulphuric acids) are sufficient to establish equilibrium rapidly in pure liquid sulphur trioxide. The present measurements provide no evidence of " ageing " of the oleums, or of other effects of this kind.

FIG. 1.



EXPERIMENTAL

General.—The vapour pressure was measured by a static method, with a glass Bourdon gauge calibrated directly as a deflection instrument. The acid was prepared by distilling sulphur trioxide, purified by several preliminary fractionations, into sulphuric acid in a flask attached to the pressure gauge in an otherwise evacuated apparatus. Concentrated oleum (*ca.* 70% of " free " sulphur trioxide) seved as a convenient source of sulphur trioxide, and was prepared by distillation of sulphur trioxide from commercial oleum in a glass apparatus at atmospheric pressure. The oleum was pre-treated with chromium trioxide to remove sulphur dioxide.

The Bourdon Gauge.—The Pyrex-glass Bourdon gauge was required to measure accurately to 0·1 mm. and to withstand pressure differences of 100 mm. The movement of the pointer was magnified optically and mechanically : a mirror, *M* (Fig. 1), suspended on needle-points at *G*, was actuated by the movement of the pointer, *H*, attached to the gauge, and the deflection of the mirror was observed on a scale at 1·3 m. The sensitivity of the assembly was controlled by the distance I—G between the needle-points and the thrust of the pointer; in most cases 1 mm. of gas deflected the image on the scale by about 3 cm., and the apparatus was sensitive to pressure changes of 0·02 mm.

* The analysis of sulphuric acid oleum is conveniently expressed in terms of the concentration of " free " sulphur trioxide, *i.e.*, sulphur trioxide present in excess of the composition H_2SO_4. In dilute oleums most of the sulphur trioxide under this heading is actually present as disulphuric acid, only a small concentration being genuinely free.

For measuring pressure up to 10 mm. the gauge was calibrated directly as a deflection instrument. Most of the recorded pressures fell in this range. At higher pressures air was admitted to the outside of the gauge, and in this case the vapour pressure was obtained as the sum of the external pressure, read on a conventional mercury manometer (15 mm. diam.), and the pressure difference across the gauge, represented by the residual deflection. The approximately linear pressure-deflection characteristic of the gauge was determined at 20° and 80° and was found to be independent of temperature. The null-point, which was slightly sensitive to temperature changes, was also determined at these temperatures and interpolated otherwise.

Preparation of Fuming Sulphuric Acid.—The apparatus is shown diagrammatically in Fig. 1. It was assembled for each run with concentrated oleum in the vessel *A* and " AnalaR " concentrated sulphuric acid in the pressure flask *E*. Dry air was used for the necessary glass-blowing. The contents of *A* were frozen to −80° and the apparatus evacuated by a two-stage mercury diffusion pump and a rotary pump. The accessible glass was heated with an oxygen flame, particularly at the constrictions used later for sealing. Without this treatment, sulphur trioxide tends to sublime on the walls of the apparatus and there is a possibility of decomposition during sealing-off.

Sulphur trioxide was distilled from *A* into *B*, and successively re-distilled into *C* and *D*. For this purpose the receiver was cooled to −80° and the distilling flask warmed gently. After each distillation the distilling flask was sealed off at a constriction and the distillate of sulphur trioxide pumped out through the tap T_1 for several hours, and finally the flask *D* was isolated from the manifold by sealing at *J*. Meanwhile the sulphuric acid in the flask *E* was degassed at 100° by pumping through T_2, and the constriction *K* was closed. To prepare the oleum, the breakable seal at *N* was opened and sulphur trioxide was distilled from *D* into *E*, the sulphuric acid in *E* being stirred and cooled in an ice-bath. Considerable pressures of sulphur trioxide developed during this distillation, which was carried out slowly to protect the guage. After distillation was complete, the contents of *E* were cooled to −80° and the constriction at *L* sealed. At this stage the null-point of the gauge was checked against earlier readings with the apparatus empty, but no measurable pressure of permanent gas was ever observed.

Throughout the distillations and the degassing the taps T_4 and T_5 were closed to prevent mercury vapour entering the system. T_1 was protected by a liquid-air trap *F* to avoid attack on the lubricant by sulphur trioxide vapour. After the pressure measurements the apparatus was opened, and the acid decanted and analysed (*J.*, 1946, 585). The gauge was found to return to its null-point when the pressures were equalised by admission of air.

Measurement of Vapour Pressure.—In general, pressures were taken at 10° intervals between 20° and 80°. During the measurements the flask and gauge were wholly immersed in a water-thermostat, controlled to ±0·05°, and the acid was stirred intermittently by an electromagnetically operated stirrer. The equilibrium value of the vapour pressure was reached in about 1 hour and was the same, within experimental error, whether approached from higher or lower temperature.

Expt. 23. Oleum, 26·7% of SO_3.

Temp. (° c)		10	20	30	40	50	60	70
Vapour pressure (mm.)	(*a*)	0·62	1·47	3·42	6·65	13·08	—	—
	(*b*)	—	1·47	3·43	6·63	13·10	25·67	49·20

(*a*), (*b*); equilibrium approached from higher and lower temp. respectively.

The system was tested for gauge errors by measuring the vapour pressure of water at 15—36°. In this experiment the gauge was sensitive to 0·1 mm. only, and the results were as follows:

Temp. (°c)	15·0	20·0	25·0	30·0	36·0
Vapour pressure (mm.)	12·8	17·6	23·7	31·9	44·6 (found)
	12·79	17·54	23·76	31·82	44·56 *

* From Landolt–Bornstein's " Tabellen."

Note on the Methods of Reading the Bourdon Gauge.—Tests showed that the gauge could be used equally well as a null or deflection instrument (Table 1). In measurements by Miles, Niblock, and Wilson (*Trans. Faraday Soc.*, 1940, **36**, 345), however, the external pressure was adjusted to bring the pointer of the gauge to an arbitrary " negative " reference mark, the pressure on the outside of the gauge being greater than the vapour pressure of the liquid under test. The compensating pressure was read on a manometer, and the vapour pressure of the liquid evaluated by subtracting the value of the external pressure required to bring the pointer to the

reference mark with zero pressure inside the gauge. But the pressure needed to move the pointer from the null-point to the " negative " reference mark actually varies with the pressure inside the gauge, and the method gives high results (Table 1, compare lines 1 and 2 with line 3). The error is fairly small, but appreciable at low pressure.

TABLE 1. *Vapour pressure reading (mm.) with positive, zero, and negative deflections of the Bourdon gauge.*

Direct deflection	5·00	14·30	20·75	44·30	74·70
Null-point	4·95	14·30	20·70	44·30	74·70
" Negative " ref. mark	5·45	14·85	21·20	44·85	75·30

DISCUSSION

There are four comparatively recent series of measurements of the vapour pressure of mixtures of sulphuric acid and sulphur trioxide. The first is due to McDavid (*J. Soc. Chem. Ind.*, 1924, **43**, 57T) who investigated oleums containing up to 40% of " free " sulphur trioxide at 40—90° by a transpiration method. The second is published in the form of a table of smoothed values in the International Critical Tables (Vol. III, p. 304; cf. Gel'fmann, *Zhur. Priklad. Khim.*, 1948, **21**, 839), no indication of the method being given. The third and fourth series are measurements by static methods. Miles, Niblock, and Wilson (*loc. cit.*) investigated six oleums in the concentration range 6—65% of sulphur trioxide, for the most part at elevated temperatures so that pressures below 12 mm. were excluded from their discussion, and Remy and Meins (*Ber.*, 1942, **75**, 1901) measured the pressures of ten oleums in the range 11—98% of sulphur trioxide at 20—40°. Some pioneer determinations were also made by Knietsch (*Ber.*, 1901, **34**, 4111) but his values do not fit with any of the later measurements. None of the published results is in quantitative agreement, although the agreement between McDavid and Miles and his co-workers is fairly good. Otherwise the differences may be very large; occasionally they represent a *factor* of ten.

The results in this paper refer to 3—35% oleum at 20—80° (Table 2). This range of

TABLE 2. *Partial pressure of sulphur trioxide in the system* H_2SO_4–$H_2S_2O_7$.

Composition, SO_3, moles %	51·1	51·5	51·5	52·9	53·1	54·3	56·0	57·9	59·4	60·8	61·0	61·7	62·5
" Free " SO_3, %	3·37	4·50	4·65	8·69	9·37	13·0	17·8	22·8	26·7	30·2	30·6	32·5	34·0
Temp.	Vapour pressure, mm.												
10°	—	—	—	—	—	—	—	0·49	0·62	—	—	—	—
20	—	—	—	—	—	0·55	0·81	1·19	1·47	2·18	2·40	3·70	5·40
25	—	—	—	—	—	0·75	—	—	—	—	—	5·15	—
30	—	—	—	0·63	0·70	0·98	1·48	2·27	3·43	4·62	5·10	7·25	7·95
35	—	—	—	—	—	1·31	—	—	—	—	—	10·1	—
40	0·52	0·52	0·54	1·10	1·25	1·77	2·85	4·63	6·65	9·34	10·9	13·9	16·3
45	—	—	—	—	—	2·43	—	—	—	—	—	19·3	—
50	0·80	0·88	0·95	2·01	2·17	3·22	5·50	8·95	13·1	18·9	21·3	26·6	32·1
60	1·33	1·56	1·68	3·65	4·08	—	10·4	17·1	26·7	36·8	40·4	—	60·2
70	2·25	2·75	2·98	6·40	7·26	—	18·5	31·4	49·2	67·2	73·1	—	109·6
80	3·82	4·84	5·26	11·2	—	—	32·3	56·6	—	—	—	—	—
$\Delta_e H$,* (kcal./mole)	(12·8)	(13·1)	(12·9)	(12·8)	(12·8)	—	13·2	13·7	13·9	13·7	13·8	(13·3)	13·5
$\Delta_e S_{298}$ (cal./mole/deg.)	—	—	—	—	—	—	44·4	45·9	46·8	46·0	46·4	44·7	45·4

Liquid SO_3. $\Delta_e H = 10·1 - 10·8$ kcal./mole.

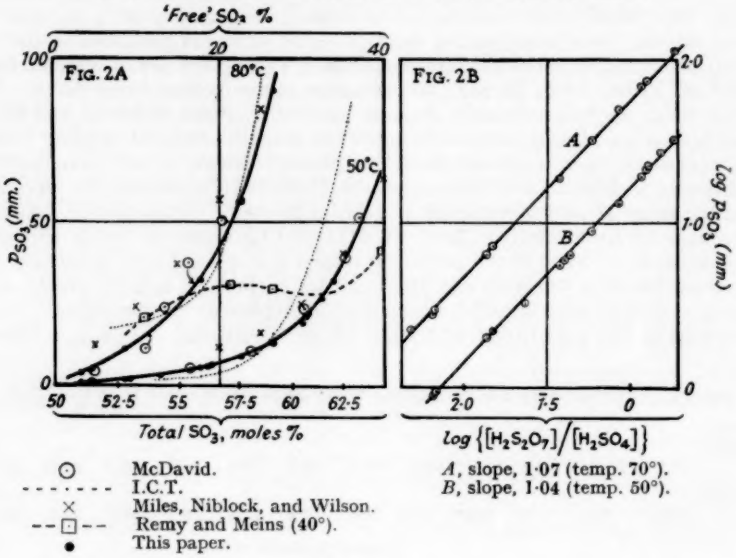
* Figures in parentheses relate to a small pressure range and are of lower accuracy.

variables overlaps in part with all the earlier series, but the results do not agree well with any of them. The best agreement is with McDavid and, although only qualitative, it is still better than between any other independent pair of measurements. On the average

McDavid's pressure differs from ours, at the same composition, by 20% (Fig. 2A) but at 50°, 60°, and 70° the correspondence is quite close. McDavid's points are scattered on both sides of our isothermals, perhaps owing partly to greater temperature fluctuation (±1°).

Where they overlap, the values of Miles, Niblock, and Wilson are higher than ours, although there is a tendency to converge near the upper limit of the common region of pressure. This is apparent in Fig. 2A, and is discussed further in a later paragraph. At the lowest pressure, Miles's results are slightly erratic (*e.g.*, at 28° the v. p. of 6·9% oleum is recorded as greater than that of 12·7%), and must be a little high on account of the technique adopted with the Bourdon gauge (Table 1) but this effect is insufficient to account for the whole difference. Apparently the optimal range of the apparatus was for pressures of the order of 100 mm., and the temperature variation of pressure, which was evaluated from the higher pressures, agrees substantially with ours.

FIG. 2. *Vapour pressure of oleum as a function of composition.*



The I.C.T. values do not fit in with the other series, both the shape of the isothermals and the temperature variation being different. The data are interpolated at regular intervals of oleum concentration and have almost certainly been smoothed with the assistance of the $\log p - 1/T$ plots. A different situation is presented by the recent results of Remy and Meins, which are very much higher than any other series and are the most difficult of all to understand. The authors state that, with the apparatus at thermal equilibrium, the pressures read with rising temperature were lower than with falling temperature, and that this behaviour was reproduced if the temperature was re-cycled. The question of whether the same limiting pressure was reached when equilibrium was approached from a higher or lower temperature was not discussed by earlier workers, but no differences were observed in our measurements (see Experimental section) and this has also been established for a closely related system, $Cl{\cdot}SO_2{\cdot}OH{-}SO_3$ (Balson and Adam, *Trans. Faraday Soc.*, 1948, **44**, 412). Another anomalous feature in Remy and Meins's account is that, even at room temperature in the range of composition 20—40%, their acids contained an asbestos-like solid, resembling β-SO_3. The solid phase is normally crystalline and is either H_2SO_4 or $H_2S_2O_7$, depending upon composition (Gable, Betz, and Maron, *J. Amer. Chem. Soc.*, 1950, **72**, 1445). Unless the results are fictitious the most reasonable explanation is that the sulphuric acid and sulphur trioxide had failed to reach equilibrium,

as suggested by the authors, but it seems doubtful if it is at all possible to reconcile Remy and Meins's values with the present vapour-pressure measurements.

The Molal Heat of Evaporation of Sulphur Trioxide.—Heats and entropies of evaporation were evaluated by the usual equation,

$$-\boldsymbol{R}\ \mathrm{d}(\ln p)/\mathrm{d}(1/\mathrm{T}) = \Delta_e H = T\Delta_e S \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The $\log p - 1/T$ plot is linear for pressures in excess of about 1 mm. (Fig. 3) and the molal heat of evaporation does not change appreciably with composition (Table 2). Both $\Delta_e H$ and $\Delta_e S$ are high relative to the values for pure sulphur trioxide and this is connected with the formation of disulphuric acid in the solution. With the most dilute oleums the logarithmic lines are curved below 1 mm., but the curvature is anomalous in that it corresponds to an apparent diminution of $\Delta_e H$ as the temperature is lowered and it is not certain that the effect is real. Miles, Niblock, and Wilson (*loc. cit.*) also analysed their results by equation (1), but their values of $\Delta_e H$ (11,300—12,500 cal.) are lower than ours,

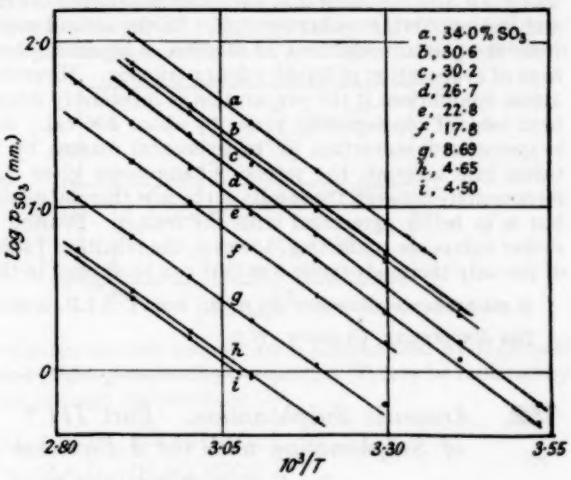


FIG. 3. *Vapour pressure of oleum as a function of temperature.*

perhaps because their measurements extended to considerably higher temperatures. Miles and his co-workers found that the logarithmic plots were curved at the lowest pressures, but the onset of curvature was at a much higher pressure (*ca.* 30 mm.) than in our experiments. In general, Miles's logarithmic plot of the measurements with dilute oleum only becomes linear near the upper limit of our pressure range, and this corresponds to the fact that the vapour-pressure measurements themselves are in improved agreement in the same region. It being granted that Miles's results are too high at the lower end of his pressure scale, the results of the two series are much more consistent than appears at first sight.

The anomalous curvature of the $\log p - 1/T$ plots is probably due to impurities present in the system. In our case about one part per million of sulphur dioxide in the oleum would exert a sufficient pressure to explain the results. Traces of sulphur dioxide were sometimes detected in the oleums but the quantities were too small for analytical estimation. The sulphur dioxide may have distilled with the sulphur trioxide, in spite of precautions, or it may have been produced by decomposition of the sulphur trioxide when the apparatus was sealed-off. A gauge of the self-degassing type may be essential at the lowest pressures.

The I.C.T. measurements give different results. The logarithmic plot is linear for all concentrations of oleum, but the values of $\Delta_e H$ change from 18,000 to 11,000 cal. in the concentration range 9—40%. This is so different from the other evidence that the pressures, particularly with the most dilute media, must be seriously in error. According to Remy

and Meins, on the other hand, the logarithmic plot is always curved and $\Delta_e H$ varies from 0 to 8000 cal. Because the heat of evaporation of liquid sulphur trioxide is about 10·5 kcal., this result means that liquid sulphur trioxide should mix *endothermally* with oleum, a conclusion which is contrary to all other evidence (including direct thermal measurements) and seems to be a decisive objection to Remy and Meins's values. It is worth noting that the authors were, apparently, unaware of the I.C.T. data and of the paper by Miles and his co-workers, and that they did not themselves evaluate $\Delta_e H$ from their results.

The heat of evaporation of sulphur trioxide from oleum has been determined by two thermal methods (Miles, Niblock, and Smith, *Trans. Faraday Soc.*, 1944, **40**, 281). A direct measurement was possible with oleums stronger than about 20% by allowing sulphur trioxide to evaporate under reduced pressure, heat being supplied to maintain constant temperature. Weaker oleums were not examined because the vapour pressure was too low and the evaporation very slow. In the range 20—30%, this experiment yielded values about 1000—1500 cal. higher than those in Table 2. The difference may be purely experimental but the thermal method is possibly open to the criticism that the rate of evaporation was small, and the result may therefore lie between the energy of activation for evaporation and the equilibrium value for $\Delta_e H$. In the second method $\Delta_e H$ was evaluated indirectly from the partial molal heat of solution of liquid sulphur trioxide in oleum and the molal heat of evaporation of liquid sulphur trioxide. However, liquid sulphur trioxide does not attain equilibrium if the preparation is intensively dried (and this was the case), and the heat content consequently varies by about 400 cal.; and, in addition, the molal heat of evaporation is uncertain for experimental reasons by the same amount. When this is taken into account, the second measurement gives $\Delta_e H = 14{,}300 \pm 500$ cal., which is intermediate between the results of the first thermal method and the vapour-pressure values but is in better agreement with the former. Bearing in mind the extent to which the earlier values are conflicting, however, the results in Table 2 seem to be satisfactory in terms of the only thermodynamic test that can be applied to them.

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THE UNIVERSITY, GLASGOW, W.2. [*Received, May 23rd*, 1952.]

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752. *Aromatic Sulphonation. Part III.* Correlation of the Velocity of Sulphonation with the J-Function of Sulphuric Acid.*

By J. C. D. BRAND and W. C. HORNING.

Velocity measurements are reported for sulphonation of $C_6H_5{\cdot}NO_2$ and p-Hal·$C_6H_4{\cdot}NMe_3^+$ in fuming sulphuric acid. The rate increases sharply with rising concentration of sulphur trioxide in the medium, and it is shown that this behaviour is consistent with the mechanism

$$ArH + SO_2{\cdot}OH^+ = Ar{\cdot}SO_2{\cdot}OH + H^+$$

The concentration of $SO_2{\cdot}OH^+$ ions in sulphuric acid is evaluated in terms of the J-function, where $J = H_0 - \log p_{SO_3}$ (cf. Gold and Hawes, *J.*, 1951, 2102), H_0 being the acidity function and p_{SO_3} the partial pressure of sulphur trioxide of the medium in question. Sulphonation *ortho* to a chloro- or bromo-substituent is appreciably retarded by steric factors.

SULPHONATION in fuming sulphuric acid always follows a simple first-order law with respect to the aromatic compound, but the apparent first-order coefficients, k_1, rise steeply and continuously with increasing concentration of sulphur trioxide in the medium. This was noted earlier for comparatively dilute oleums (Part II, *J.*, 1950, 1004) and the measurements have now been extended by the investigation of less reactive molecules in more concentrated media. It will be shown that the experimental results are consistent with the mechanism

$$ArH + SO_2{\cdot}OH^+ = Ar{\cdot}SO_2{\cdot}OH + H^+ \quad . \quad . \quad . \quad . \quad . \quad (1)$$

* Part II, *J.*, 1950, 1004.

and that the variation of k_1 is determined essentially by the variation with medium composition of the concentration of the $SO_2{\cdot}OH^+$ cation.

The concentration of $SO_2{\cdot}OH^+$ is deduced formally from equilibrium (2)

$$HO{\cdot}SO_2{\cdot}O{\cdot}SO_2{\cdot}OH + H^+ \overset{K_1}{\rightleftharpoons} HO{\cdot}SO_2{\cdot}OH + SO_2{\cdot}OH^+ \quad . \quad . \quad . \quad . \quad (2)$$

the equilibrium constant, K_1, being given by

$$K_1 = (\{SO_2{\cdot}OH^+\}\{H_2SO_4\})/(\{H_2S_2O_7\}\{H^+\}) \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where the braces { } refer to activities relating to the standard state of an infinitely dilute solution in sulphuric acid. $\{H^+\}$ in equation (3) is eliminated by introducing the definition of the acidity function

$$H_0 = A - \{H^+\} \log (f_B/f_{BH^+}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where BH^+ and B represent the acid–base pair used in the measurement of H_0 and the f's refer to the standard state in sulphuric acid. The term A is constant at constant temperature and takes care of the fact that H_0 is usually defined with reference to a standard state in water (Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1939); the circumstance that a single constant will transfer from one standard state to another is equivalent to the assumption that the ratio f_B/f_{BH^+} has the same value in a given medium

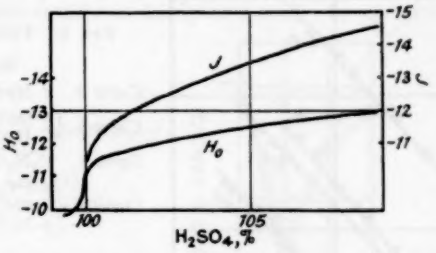

FIG. 1. H_0 *and* J*-functions of fuming sulphuric acid.*

for all bases, and the supporting evidence for this assumption is summarised by Hammett (*loc. cit.*). In addition, $\{H_2S_2O_7\}$ and $\{H_2SO_4\}$ appearing in equation (3) may be replaced by experimentally accessible quantities through the relations (5)

$$\left.\begin{aligned} H_2SO_4 + SO_3 &\overset{K_2}{\rightleftharpoons} H_2S_2O_7 \\ K_2 &= \{H_2S_2O_7\}/\{H_2SO_4\}\{SO_3\} \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

and substitution in equation (3) by means of (4) and (5) yields the expression (6) for the concentration of $SO_2{\cdot}OH^+$.

$$\log [SO_2OH^+] = \log \{SO_3\} - H_0 - \log (f_B/f_{BH^+}){\cdot}f_{SO_2{\cdot}OH^+} + A + \log (K_2K_1) \quad . \quad (6)$$

If we define the activity of sulphur trioxide in sulphuric acid solution to be equal to its vapour pressure, and write $J = H_0 - \log (P_{SO_3})$, by analogy with the J_0 function for aqueous sulphuric acid introduced by Gold and Hawes (*J.*, 1951, 2102), equation (6) becomes simply

$$\log [SO_2OH^+] = -J - \log (f_B/f_{BH^+}){\cdot}f_{SO_2{\cdot}OH^+} + A + \log (K_1K_2) \quad . \quad . \quad (7)$$

On the basis of equation (1), the velocity of sulphonation is given by

$$-\mathrm{d}[ArH]/\mathrm{d}t = k[ArH][SO_2OH^+]{\cdot}f_{ArH}{\cdot}f_{SO_2{\cdot}OH^+}/f^*$$

f^* denoting the activity coefficient of the transition state. From the fact that the reaction is experimentally of the first order it follows that

$$-\mathrm{d}[ArH]/\mathrm{d}t = k_1[ArH]; \quad k_1 = k[SO_2{\cdot}OH^+](f_{ArH}{\cdot}f_{SO_2{\cdot}OH^+}/f^*) \quad . \quad . \quad (8)$$

Combination of the equations (7) and (8) yields equation (9)

$$\log k_1 = -J + \log (f_{ArH}/f^*)/(f_{BH^+}/f_B) + [\log k + \log (K_1K_2) + A] \quad . \quad . \quad (9)$$

which expresses the variation of the experimental velocity coefficient, k_1, with medium composition in terms of the J-function (Fig. 1) and an activity coefficient term of

approximately symmetrical form. The final term in equation (9), in square brackets, is constant at constant temperature because k, K_1, and K_2 are thermodynamic constants.

Equation (9) is applied to the experimental results (Tables 2 and 3, and Part II) in Fig. 2. If the mechanism represented by (1) is correct, and if the activity coefficient term in equation (9) is zero, the points should fall on a straight line of unit slope. In practice, straight lines through the experimental points have slopes varying from 1·03 for nitrobenzene (curve *c*) to 1·16 for the trimethylphenylammonium ion (curve *b*). The results cover an effective variation of velocities of several powers of ten and provide a reasonably comprehensive test; in fact, it is not certain that the deviation from unit slope exceeds the experimental error in J. However, although there are excellent reasons for believing that the activity-coefficient term in (9) is small, it is probably too simple, in view of the large alteration of medium composition, to assume that it is actually zero; but if the term is non-zero it is more difficult to decide whether it is positive or negative. An immediate argument is that, in the case of nitration in fuming sulphuric acid, the term $f_{ArH}{\cdot}f_{NO_2^+}/f^{\ddagger}$ is known experimentally to increase with rising sulphur trioxide concentration,* *i.e.*, its

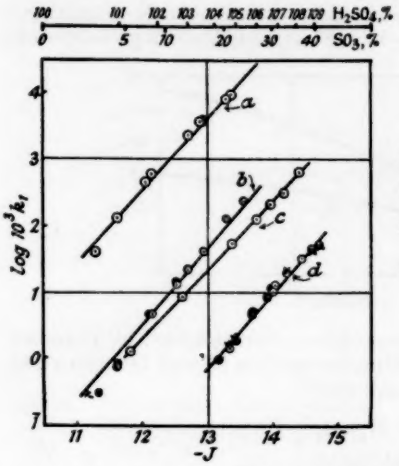

FIG. 2. *Velocity of sulphonation as a function of* J.

	Reactant		Ordinate	Slope
Curve a.	*p*-Me·C_6H_4·NO_2		log 10^3k_1	1·07
Curve b.	*p*-Me·C_6H_4·NMe_3^+	●	log 10^3k_1 − 2·56	1·16
	C_6H_5·NMe_3^+	⊙	log 10^3k_1	
Curve c.	C_6H_5·NO_2		log 10^3k_1	1·03
Curve d.	*p*-F·C_6H_4·NMe_3^+	×	log 10^3k_1	1·14
	p-Cl·C_6H_4·NMe_3^+	⊙	log 10^3k_1	
	p-Br·C_6H_4·NMe_3^+	●	log 10^3k_1 − 0·11	

logarithm is positive. The analogy is not complete, but it does not seem unreasonable that log $(f_{ArH}/f^{\ddagger})/(f_{BH^+}/f_B)$ should also be positive, and the slopes of the lines in Fig. 2 therefore slightly greater than unity.

Two points of detail may be mentioned here. First, in the substitution of derivatives of $C_6H_5{\cdot}NMe_3^+$, ArH in equation (9) stands for an ion of unit charge and the transition state is a doubly-charged dipolar ion, so that the symmetry of the activity coefficient term is not immediately apparent. But there are experimental reasons for believing that the ratios $f_{^+B}/f_{^+BH^+}$ and f_B/f_{BH^+} (where ^+B and B represent a charged and an uncharged base respectively) vary in a similar way in solvents of high dielectric constant (Brand, Horning, and Thornley, *J.*, 1952, 1374) and it can be argued, therefore, that $f_{ArH}/f^{\ddagger}$ will be approximately the same for a charged and an uncharged reactant. Supporting evidence is provided by the fact that the relative velocity of nitration of $C_6H_5{\cdot}NMe_3^+$ and $C_6H_5{\cdot}NO_2$ in sulphuric acid is independent of medium (Bonner, James, Lowen, and Williams, *Nature*, **1949**, **163**, 955), because this must mean that the ratios $f_{Ph{\cdot}NMe_3^+}/f^{\ddagger(2+)}$ and $f_{Ph{\cdot}NO_2}/f^{\ddagger(+)}$ vary with medium conposition in the same way. Secondly, it is obvious from Fig. 2 that the nitro-compounds furnish slopes nearer unity than do the quaternary ammonium systems. This may be due partly to the greater symmetry of the activity coefficient quotient, but it is more probably explained by the fact that the H_0 scale, which is the least certain of the experimental quantities, enters twice into the correlation of log k_1 with J, so that the errors

* It is interesting that the most rapid rise occurs in 101—102% media, because it is in the same region of composition that the points in Fig. 2 tend to deviate from linearity.

in H_0 tend to balance out. The nitro-compounds are extensively ionised in the sulphuric acid medium, and the H_0 scale is used to evaluate the degree of ionisation, so that the velocity of sulphonation can be referred to the un-ionised molecules only (Parts I and II). The quaternary ammonium systems, of course, are not involved in an acid–base equilibrium of this kind.

The correlation in Fig. 2 shows that the velocities are consistent with the mechanism represented by (1), but the argument is too general to be regarded as an unequivocal proof of mechanism. Some alternatives can be eliminated: *e.g.*, neither monomolecular SO_3 (velocities correlated with partial pressure) nor $H_3SO_4^+$ (correlation with H_0) is possible. However, because H_0 and log (p_{SO_3}) are almost parallel functions of the medium composition (cf. Lewis and Bigeleisen, *J. Amer. Chem. Soc.*, 1943, **65**, 1144), log k_1 could be correlated successfully with $2H_0$ or with 2 log (p_{SO_3}) instead of J, all three functions having similar relative values. The first possibility corresponds to sulphonation by $H_4SO_4^{++}$ (too improbable to be considered further), the second to S_2O_6. An argument for preferring $SO_2{\cdot}OH^+$ to S_2O_6 in oleum is that it explains the exceptional power of sulphuric acid as a sulphonating medium, in terms of the high proton-activity of the solution; this is particularly striking if it is remembered that the presence of sulphuric acid is in other respects unfavourable, because the equilibrium $SO_3 + H_2SO_4 \rightleftharpoons H_2S_2O_7$ causes a large proportion of the sulphur trioxide to be stored unprofitably as disulphuric acid. In aprotic solvents

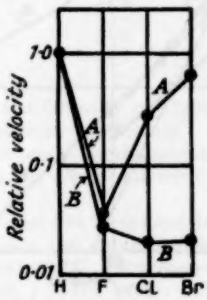

FIG. 3. *Relative velocities of substitution of* p-Hal·C_6H_4·NMe_3^+.

Curve A. Nitration in H_2SO_4.
Curve B. Sulphonation in H_2SO_4.

however, there is kinetic evidence in favour of S_2O_6 (Hinshelwood and his co-workers, *J.*, 1939, 1372; 1944, 469, 649), and S_2O_6 is even analogous to $SO_2{\cdot}OH^+$ in the general system of acids and bases.

Steric Retardation of Sulphonation.—The relative velocity of sulphonation of derivatives of $C_6H_5{\cdot}NMe_3^+$ is practically independent of the medium composition, and this condition is also satisfied for nitration in sulphuric acid (Bonner, James, Lowen, and Williams, *loc. cit.*); the effect of the greater size of the sulphonating agent can therefore be seen by comparing directly the relative velocities of nitration and sulphonation (Table 1). It seems reasonable to suppose that, apart from the size factor, the influence of the halogens should be quali-

TABLE 1. *Relative velocities of substitution of* p-Hal·C_6H_4·NMe_3^+ *in sulphuric acid (at 25°).*

	H	F	Cl	Br
Nitration *	1·0	0·030	0·165	0·32
Sulphonation	1·0	0·026	0·020	0·022

* Brand and Paton, *J.*, 1952, 281.

tatively in the same order for both sulphonation and nitration. In the examples given in Table 1, with the exception of the parent compound, the point of attack is *ortho* to the halogen substituent; and, sulphonation being compared with nitration, the results give a clear indication of steric compression in the transition state of sulphonation of the chloro- and bromo-derivatives (Fig. 3). A fluoro-substituent does not impede sulphonation appreciably. The iodo-compound does not react smoothly in sulphuric acid solution, and velocity measurements are not available.

Experimental

Materials.—p-*Fluorophenyltrimethylammonium methyl sulphate*, prepared from *p*-fluorodimethylaniline and methyl sulphate in acetone, had m. p. 104·5° (Found: C, 45·1; H, 5·9; N, 5·4. $C_{10}H_{16}O_4NFS$ requires C, 45·3; H, 6·1; N, 5·3%). p-*Iodophenyltrimethylammonium methyl sulphate*, prepared similarly, had m. p. 185° (decomp.) (Found: C, 32·4; H, 4·3; N, 3·9. $C_{10}H_{16}O_4NIS$ requires C, 32·2; H, 4·3; N, 3·75%), but decomposed too readily in sulphuric acid solution for velocity measurements to be undertaken.

Velocity Measurements.—The velocity of sulphonation of nitrobenzene was determined directly from the change of transmission at 3650 Å (Table 2). Owing to the fact that the nitrobenzene is present in the solution as phenylnitracidium cation the reaction is attended by a large, approximately 20-fold, decrease in ε at this wave-length, corresponding to the replacement of $C_6H_5{\cdot}NO{\cdot}OH^+$ by $NO_2{\cdot}C_6H_4{\cdot}SO_3H$. Protonisation of the nitrobenzenesulphonic acid only occurred to an appreciable extent in the most powerfully acidic media (>35% oleum). The reaction was conducted in optical cells (depth, 1 cm.), fitted with side-arms and stoppers, immersed in a small tank through which water circulated at 25°. The tank was provided with glass windows and was placed in the cell-compartment of a Hilger " Spekker " absorptiometer. The

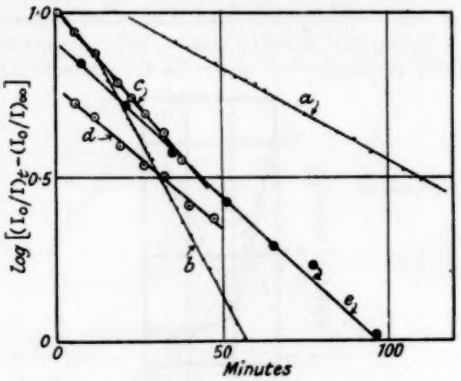

Fig. 4. *Spectrophotometric velocity coefficients for sulphonation in fuming sulphuric acid.*

Curve a, $C_6H_5{\cdot}NO_2$ (108·22% H_2SO_4), k_a = 0·0129 min.$^{-1}$.

Curve b, p-$CH_3{\cdot}C_6H_4{\cdot}NO_2$ (103·43% H_2SO_4), k_a = 0·0438 min.$^{-1}$.

Curve c, p-$F{\cdot}C_6H_4{\cdot}NMe_3^+$ (107·45% H_2SO_4), k_1 = 0·0282 min.$^{-1}$.

Curve d, p-$Cl{\cdot}C_6H_4{\cdot}NMe_3^+$ (107·45% H_2SO_4), k_1 = 0·0198 min.$^{-1}$.

Curve e, p-$Br{\cdot}C_6H_4{\cdot}NMe_3^+$ (107·45% H_2SO_4), k_1 = 0·0212 min.$^{-1}$.

apparent velocity coefficients, k_a, were evaluated by plotting log {log $(I_0/I)_t$ − log $(I_0/I)_\infty$} (where the I's are intensities and the subscripts refer to time) against time (Fig. 4). The true velocity coefficients, k_1 (Table 2, col. 6), are referred to the concentration of *un-ionised* nitrobenzene only

Table 2. *Influence of medium on the rate of sulphonation (at 25°).*

Medium						
H_2SO_4, %	SO_3, %	10^5k_a (min.$^{-1}$)	$-H_0$	Fraction of un-ionised nitrobenzene	10^5k_1 (min.$^{-1}$)	$-J$
		Nitrobenzene, pK_a = − 11·26.*				
101·27	5·66	0·305	11·77	0·236	1·29	11·83
102·77	12·3	1·07	12·11	0·123	8·69	12·60
104·77	21·2	3·16	12·46	0·059	53·3	13·36
106·07	27·0	5·29	12·58	0·042	126	13·75
106·75	30·0	7·25	12·71	0·034	212	13·96
107·33	32·6	8·60	12·80	0·028	308	14·16
108·22	36·6	12·8	12·95	0·020	640	14·40
		p-*Nitrotoluene*, pK_a = − 10·34.*				
103·43	15·2	43·9	12·25	0·0121	3630	12·88
104·70	20·9	70·6	12·46	0·0075	9420	13·36

* Brand, Horning, and Thornley, *loc. cit.*

and are evaluated by using the ionisation data of Brand, Horning, and Thornley (*loc. cit.*). The overall rate of sulphonation of nitrobenzene (k_a) in concentrated oleum is actually lower than that of the quaternary systems p-Hal·$C_6H_4{\cdot}NMe_3^+$, owing to the immobilisation of a high proportion of the nitrobenzene as an unreactive cation (Fig. 4).

The values of the velocity coefficient, k_1, for un-ionised nitrobenzene are slightly *lower* than the results for the trimethylphenylammonium cation in the same medium, instead of being

slightly higher as reported in Part II. This is due to a revision of the H_0 scale; it is important to emphasise that H_0 is much more uncertain experimentally than the velocity coefficients.

The quaternary ammonium ions were added as crystalline methyl sulphates to the sulphonating medium, and the progress of the reaction was followed by an indirect method. Aliquot portions of the reaction mixture were withdrawn by pipette, and the sulphonation arrested by running the mixtures into solutions of potassium nitrate in *ca.* 85% sulphuric acid. The unsulphonated quaternary ammonium ions were nitrated slowly but quantitatively, the sulphonic acid being unattacked under these conditions, and the nitro-compound was then estimated from the transmission of the solution in a spectral region (3200—3400 Å) where the nitro-group absorbed strongly but where the other constituents of the solution were transparent. The optical density at these wave-lengths was proportional to the concentration of unsulphonated material, and k_1 could be evaluated directly. The mean results are collected in Table 3.

TABLE 3. *Influence of medium on the rate of sulphonation of* p-Hal·C_6H_4·NMe_3^+ (*at* 25°).

Medium		10^3k_1 (min.$^{-1}$) for			
H_2SO_4, %	SO_3, %	F	Cl	Br	$-J$
104·18	18·6	—	—	0·959	13·16
104·70	20·9	2·1	1·45	—	13·33
105·00	22·2	2·66	—	1·92	13·44
105·81	25·9	6·10	4·59	4·63	13·68
106·54	29·1	11·1	8·60	—	13·91
106·76	30·1	—	10·5	11·6	13·99
106·89	30·6	—	13·2	—	14·02
107·45	33·1	28·3	19·9	21·2	14·21
108·88	39·5	50	45·1	50·7	14·60
109·23	41·0	65	52	—	14·71

Initial concentrations were 10^{-3}—10^{-4}M, depending on the intensity of absorption. Under these conditions individual experiments always yielded first-order coefficients. A low reactant concentration was desirable because quite small concentrations of methosulphate ions exert a pronounced retardation (Part II), but in the present case the effect was within the limits of experimental error.

J-Function of Fuming Sulphuric Acid (Fig. 1).—The J-function is defined by the equation $J = H_0 - \log(p_{SO_3})$ (cf. Gold and Hawes, *loc. cit.*). Because the vapour pressure of sulphur trioxide in dilute oleum is too small for accurate measurement at 25°, J has been evaluated from vapour-pressure measurements at 50° (Brand and Rutherford, *J.*, 1952, 3916). This treatment is justified because the gradient of the log (p_{SO_3}) plot is independent of the composition of the medium, and the *relative* values of J are therefore independent of the temperature to which the vapour-pressure measurements refer, provided they always refer to the same temperature. The J-function in this paper is purely relative, in the sense that the definition attaches no significance to the absolute values.

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753. *Aromatic Sulphonation. Part IV.* Isomeric Ratios in the Sulphonation of Trimethyl-phenyl- and -p-tolyl-ammonium Methyl Sulphates.*

By J. C. D. BRAND and A. RUTHERFORD.

Sulphonation of the ion p-CH_3·C_6H_4·NMe_3^+ occurs quantitatively in the *m*-position with respect to the quaternary ammonium group. Sulphonation of C_6H_5·NMe_3^+ yields an inhomogeneous mixture of at least three components, including the products of sulphonation in the *m*- and the *p*-position; quantitative analysis is attempted on the basis of solubility measurements.

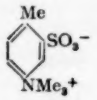
SULPHONATION of the trimethylphenylammonium and trimethyl-*p*-tolylammonium ions has not been examined previously. The ions react smoothly with fuming sulphuric acid, the consumption of sulphur trioxide is theoretical, and quantitative yields are obtained.

* Part III, preceding paper.

In the sulphonation of the trimethylphenylammonium ion, *m*-, *p*-, and (probably) *o*-isomerides are formed. The relevant observations may be summarised as follows.

(*a*) p-$CH_3 \cdot C_6H_4 \cdot NMe_3^+$.—The product is chemically homogeneous and has the empirical composition $C_{10\cdot0}H_{15\cdot9}O_{3\cdot1}N_{1\cdot01}S_{0\cdot98}$. The homogeneity follows from the fact that the first and the last fraction of a fractional crystallisation possess the same solubility, and further solubility measurements show that the substance is identical with the " betaine " (I).

(*b*) $C_6H_5 \cdot NMe_3^+$.—The product has the empirical composition $C_{9\cdot0}H_{13\cdot0}O_{2\cdot8}N_{1\cdot03}S_{1\cdot02}$, but is not homogeneous because the solubility of successive fractions from a crystallisation rises continuously. The presence of trimethyl-*m*- and -*p*-sulphophenylammonium " betaines " (II) and (III) can be established by solubility measurements, but the product is not insoluble in a solution saturated simultaneously with both, and must therefore contain at least *three* components. Attempts to prepare the *o*-sulpho-compound were unsuccessful because mild methylating conditions were ineffective owing to the steric



(I) m-$^+NMe_3 \cdot C_6H_4 \cdot SO_3^-$ (II) p-$^+NMe_3 \cdot C_6H_4 \cdot SO_3^-$ (III)

compression and vigorous conditions procured rearrangement. However, by assuming that the third constituent is the *o*-isomeride (which is consistent with the elemental analysis and the failure of the product to give any reactions of a tertiary amine or other likely decomposition product), the composition of the product can be shown semiquantitatively to be *o* 8, *m* 78, and *p* 14%. Details are given in the Experimental section.

It is interesting that the $C_6H_5 \cdot NMe_3^+$ ion, which is nitrated exclusively in the *m*-position (Vorländer and Siebert, *Ber.*, 1919, **52**, 283; cf. Goss, Hanhart, and Ingold, *J.*, 1927, 250; Ingold, Shaw, and Wilson, *J.*, 1928, 1280), yields a mixture of isomerides on sulphonation. The sulphonating agent is apparently less powerfully electrophilic than the nitronium cation. Ostensibly this might mean that the reagent is uncharged, but the kinetics point strongly to the conclusion that the $SO_2 \cdot OH^+$ cation is the effective sulphonating agent in oleum media (Part III, preceding paper); probably the explanation is that the formal charge on the large and polarisable sulphur atom is more effectively screened than is the case with NO_2^+.

Experimental

Materials.—Trimethyl-phenyl- and -*p*-tolyl-ammonium methyl sulphates were prepared by combination of the tertiary amine with methyl sulphate in acetone, recrystallised from alcohol–acetone, and dried *in vacuo* over phosphoric oxide. They had, respectively, m. p. 126° (Found : SO_4, 38·6. Calc. for $C_{10}H_{17}O_4NS$: S, 38·8%) and 144·5° (Found : SO_4, 36·7. Calc. for $C_{11}H_{19}O_4NS$: S, 36·7%), being analysed by estimation of $SO_4^=$ as barium sulphate after hydrolysis with concentrated hydrochloric acid at 100°.

*Trimethyl-2-sulpho-*p*-tolylammonium betaine* (Me = 1) (I) was obtained by methylation of 4-aminotoluene-2-sulphonic acid with methyl iodide and sodium carbonate in aqueous solution (Devoto and Ardissone, *Gazzetta*, 1934, **64**, 371). After evaporation, the betaine was separated from inorganic salts by extraction with 95% alcohol, and purified by further recrystallisations from aqueous alcohol. The *monohydrate* was obtained by drying *in vacuo* (Found : C, 48·8; H, 6·8; N, 5·9; S, 13·0; H_2O, 7·4. $C_{10}H_{15}O_3NS,H_2O$ requires C, 48·6; H, 6·9; N, 5·7; S, 13·0; H_2O, 7·3%), and the anhydrous betaine at 110° (Found : C, 52·2; H, 6·6; N, 6·3; S, 13·7. $C_{10}H_{15}O_3NS$ requires C, 52·4; H, 6·6; N, 6·1; S, 14·0%). Trimethyl-*m*-sulphophenyl ammonium betaine (II) (Found : C, 50·4; H, 6·1; N, 6·8; S, 14·7. Calc. for $C_9H_{13}O_3NS$: C, 50·2; H, 6·1; N, 6·5; S, 14·9%) and trimethyl-*p*-sulphophenyl ammonium betaine (III) (Found : C, 50·2; H, 5·9; N, 6·4; S, 15·2%) were readily prepared from metanilic and sulphanilic acid respectively by the same method.

Potassium *o*-dimethylaminobenzenesulphonate, prepared by methylation of *o*-aminobenzenesulphonic acid with methyl sulphate and potassium hydroxide, was converted through the barium salt into *o*-dimethylaminobenzenesulphonic acid (cf. Bamberger and Tschirner, *Ber.*, 1899, **32**, 1882) (Found : C, 47·6; H, 5·5; N, 7·3; S, 16·2%; *M*, 201·6. Calc. for $C_8H_{11}O_3NS$: C, 47·7; H, 5·5; N, 7·0; S, 15·9%; *M*, 201·3).

In an attempt to prepare trimethyl-*o*-sulphophenylammonium betaine, *o*-dimethylaminobenzenesulphonic acid was brought into solution in methyl sulphate (2 mols.) by refluxing for 1 hour. Dilution with alcohol yielded trimethyl-*p*-sulphophenyl-ammonium betaine, showing that "migration" of the sulpho-group had occurred. (Compare the conversion of *o*-aminobenzenesulphonic acid into sulphanilic acid by hot sulphuric acid; Bamberger and Kronig, *Ber.*, 1897, **30**, 2276.) The identity of the betaine was established by the fact that its co-solubility with (III) was zero.

Refluxing *o*-aminobenzenesulphonic acid (3·5 g.) with excess of methyl sulphate (13 ml.) also led to rearrangement and yielded 25—30% of methyl *p*-dimethylaminobenzenesulphonate, m. p. 91° (from benzene–light petroleum or aqueous methanol). Houben and Schreiber's assumption (*Ber.*, 1920, **53**, 2346) that the product of this experiment is methyl *o*-dimethylaminobenzenesulphonate is mistaken; that the ester formed belongs to the *p*-series is proved by the ultraviolet absorption spectrum (log $\varepsilon_{max.}$ = 4·38 at 2750 Å) in which there is no evidence of steric compression characteristic of *o*-compounds of this type. Methyl *p*-dimethylaminobenzenesulphonate can be prepared directly from sulphanilic acid and methyl sulphate, and is identical with the above product. Conversion of this ester into trimethyl-*p*-sulphophenylammonium betaine (III) occurs slowly at room temperature and rapidly above the m. p., as described also by Kuhn and Ruelius (*Chem. Ber.*, 1950, **83**, 244).

Heating *o*-dimethylaminobenzenesulphonic acid with methyl iodide and aqueous methanol at 110° led to hydrolysis of the sulphonate group. The difficulty of preparing the *o*-betaine by these methods is due as much to the ease of rearrangement and hydrolysis as to the steric hindrance to formation of the quaternary ammonium group.

Consumption of Sulphur Trioxide.—The sulphur trioxide consumed during sulphonation of trimethyl-*p*-tolylammonium methyl sulphate was determined by titrating the solution with water after complete reaction. Allowance was made for immobilisation of 0·5 mol. of sulphur trioxide by the betaine formed (*J.*, 1946, 880).

a = Moles of water added to 1000 g. of oleum.
b = Reduction in water-titre, moles per 1000 g. of oleum.

a	*b*	*b*/*a*	*a*	*b*	*b*/*a*
p-$C_7H_7{\cdot}NMe_2.SO_4Me$			1 : 2 : 4-Me·$C_6H_3(SO_3^-)NMe_3^+$		
0·060	0·109	1·82	0·054	0·028	0·52
0·133	0·207	1·56	0·097	0·045	0·46
0·161	0·213	1·32	0·126	0·063	0·50
0·166	0·249	1·50	0·152	0·085	0·56
0·210	0·317	1·51	0·215	0·112	0·52
0·249	0·366	1·47	0·218	0·100	0·46
	r.m.s. av.:	1·49			0·50

The reaction consumes $1{\cdot}4_0 - 0{\cdot}5_0 = 0{\cdot}9_0$ mole of SO_3 per mole of reactant.

Isolation of the Products.—The product was separated from sulphuric acid by the usual methods. In a typical experiment (Expt. A, Table 1) trimethyl-*p*-tolylammonium methyl sulphate (12·02 g.) reacted with 15% fuming sulphuric acid (74 g.) for 24 hours at 25°. The mixture was then diluted to 12N-sulphuric acid and heated on the water-bath to hydrolyse the

TABLE 1.

	Medium		Reactant		Time,	Recovery of product	
Expt.	Concn. of "free" SO_3. %	g.		g.	hrs.	g.	%
A	15	74	$C_7H_7{\cdot}NMe_2.SO_4Me$	12·02	24	10·47	99·2
B	15	26	Betaine (I)	3·64	22	3·58	96·8
C	25	56	$Ph{\cdot}NMe_2.SO_4Me$	13·9	232	12·34	100·2
D	25	20	,,	5·00	15	2·68	(63·4) *

* Expt. D was interrupted before sulphonation was complete.

methyl hydrogen sulphate, then diluted further, neutralised with barium carbonate, filtered, and evaporated. The residue, after being washed with alcohol, was colourless and crystalline (10·63 g.), the only impurity being a little inorganic material (0·162 g., chiefly sodium sulphate) introduced with the barium carbonate; the yield of betaine (I) was 99·2%. The sodium sulphate was removed by one recrystallisation from aqueous alcohol (Found: C, 52·1; H, 6·9; N, 6·2%).

Other results are summarised in Table 1. Expt. B showed that the reaction product could be recovered unchanged from the sulphonating medium; migration of the sulphonate group does not occur in the systems with an NMe_3^+ substituent. Expt. D was interrupted at approximately two-thirds reaction to determine whether the product composition was the same as that found after complete reaction; this proved to be the case (Table 3).

Solubility Measurements.—The components were shaken mechanically in a stoppered flask in a thermostat for sufficient time to attain equilibrium (1—2 hours). Samples of the liquid phase were withdrawn through a filter by means of a pipette, and the solubility was determined by weighing the residue after evaporation. Aqueous ethanol was used as solvent. The results are in Tables 2 and 3. It was found that the product from the ion p-C_7H_7·NMe_3^+ was entirely homogeneous, apart from the inorganic material introduced during the working up, and was (I). In the case of the Ph·NMe_3^+ ion, however, formation of the betaines (II) and (III) was readily established (Table 3, lines 4—6), and in the following discussion the remainder, which was not identified directly, is assumed to be the *o*-isomeride.

TABLE 2. *Sulphonation of* p-C_7H_7·NMe_3^+ *: co-solubility of the product with* (I) (65% *ethanol*; 20°).

Solid		Solubility (g./100 g. of soln.)		
	wt. (g.) equilibrated with 10 ml. of solvent	total	inorganic	organic
Betaine (I) alone	1·591	3·35	—	3·35
Betaine (I) + product of expt. A	>0·4	3·36	—	3·36
	1·504 *			
Betaine (I) + product of expt. A	>0·4	3·49	0·14	3·35
	1·519			
Betaine (I) + product of expt. B	>0·4	3·50	0·15	3·35
	1·520			

* After one recrystallisation.

Even if the assumption is granted that the *o*-isomeride completes the range of products from the Ph·NMe_3^+ ion, the proportions still cannot be calculated from the co-solubility with (II) and (III) unless the mutual solubility effects are made the subject of a separate assumption. We assume (*a*) that in a solution saturated simultaneously with (II) and (III) the components are present in the ratio of their individual solubilities, and (*b*) that in computing the increment of the solubility of the *m*-isomeride in a ternary solution the *o*- and the *p*-isomeride can be counted together and the solution treated as binary. This is a crude argument, and the results can only be semi-quantitative. On the basis of these assumptions and by insertion of numerical values from Table 3 (lines 1—3), the solubility, S_m, of the *m*-isomeride in the presence of w g. of the (o + p)-isomerides is given by

$$S_m = 8{\cdot}25 + (8{\cdot}68 - 8{\cdot}25)w/(9{\cdot}45 - 8{\cdot}68) = 8{\cdot}25 + 0{\cdot}558w$$

The total solubility, S_t, is therefore

$$S_t = S_m + w = 8{\cdot}25 + 1{\cdot}558w$$

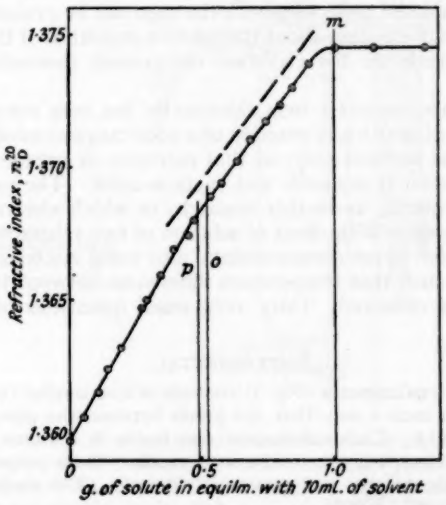
and by this equation we may calculate w from S_t, subject to the two previous assumptions. For the two solutions at the foot of Table 3 (S_t = 9·76 and 9·10 g. per 100 g. of solvent), we obtain $w = 0{\cdot}97_0$ g. and $0{\cdot}54_7$ g.; S_m is, therefore, 8·79 and 8·55 g. per 100 g. of solvent, respectively. Hence, from the result in the last line of Table 3, the yield of (o + p)-isomers per 2·38 g. of reaction product is 9·10 − 8·55 = 0·55 g., or 23·1%. Similarly, from the penultimate line, the percentage yield of *o*-isomer is 100[9·76—(8·79 + 0·77)]/2·42 = 8·3. The percentage yield of *p*-isomer is 23·1 − 8·3 = 14·8.

The results of this calculation were tested for internal consistency in the following way. Successively increasing amounts of the reaction product were shaken with solvent and the refractive index of the solution determined at equilibrium after each addition (Figure). A change of slope of the curve relating refractive index to the total weight of solid occurred when the system became saturated with respect to one of the constituents. The points at which this should occur were also calculated from the product composition in Table 3, the location of the predicted alterations of slope being shown in the Figure. The solution appears to become saturated almost simultaneously with the *o*- and the *p*-isomeride. The gradient of the central

TABLE 3. *Sulphonation of* $Ph{\cdot}NMe_3^+$ *: co-solubility of the product with* (II) *and* (III) (55% *ethanol*; 25°).

Solid	wt. (g.) equilibrated with 100 g. of solvent	Solubility * (g. per 100 g. of solvent)	Isomeric composition of product, %		
			m	*p*	*o*
Betaine (III) alone	Excess †	0·735	—	—	—
Betaine (II) alone	Excess	8·25	—	—	—
Betaines (II) and (III)	,,	9·45	—	—	—
Betaine (II) + product of expt. C	,,	10·2	—	—	—
Betaines (II) & (III) + product of expt. C	,,	10·2	—	—	—
Product of expt. C	14·7	$10{\cdot}2_3$	—	—	—
	12·8	$10{\cdot}2_2$	—	—	—
Betaines (II) & (III) + product of expt. C	Excess				
	2·45	9·77	78	14	8
Betaine (II) only + product of expt. C	Excess				
	2·45	9·08			
Betaines (II) & (III) + product of expt. D	Excess				
	2·42	9·76	77	15	8
Betaine (II) only + product of expt. D	Excess				
	2·38	9·10			

* Excluding inorganic material (cf. Table 2). † *I.e.*, sufficient to ensure saturation.



portion of the curve, where the solution is unsaturated only with respect to the *m*-isomeride, could be calculated from the refractive index of a saturated solution of the pure *m*-isomeride and the proportion of *m*-compound in the reaction product, and is shown in the Figure by a broken line displaced on the ordinate for the sake of clarity. The agreement is only approximate, but seems in both cases to be satisfactory.

A maintenance allowance (to A. R.) by D.S.I.R. is gratefully acknowledged.

THE UNIVERSITY, GLASGOW, W.2. [*Received, May 23rd,* 1952.]

754. *A New Twin Micro-calorimeter, and the Heat of Transformation of α- into β-Quinol.*

By D. F. Evans and R. E. Richards.

A new twin micro-calorimeter is described, in which differential or direct heats of solution can be measured accurately. The calorimeter is vacuum- and pressure-tight, and the solutions come into contact with glass surfaces only. The heat of solution of potassium chloride in water has been measured. The preparation of β-quinol is described, and the heat of formation from α-quinol measured. For α-quinol (solid) ⟶ β-quinol (solid), $\Delta H = 0{\cdot}13 \pm 0{\cdot}03$ kcal./mole.

Quinol exists in three crystalline modifications, referred to as the α-, β-, and γ-forms; the α-form is the common one. β-Quinol can be obtained under special conditions from alcoholic solutions (see p. 3935) and is the modification which forms the lattice cage in the "clathrate" compounds described by Palin and Powell (*J.*, 1948, 815). γ-Quinol can be obtained by sublimation of α-quinol.

The heat of the transition of α- into β-quinol has now been measured, so that when this is combined with heats of formation of clathrate compounds relative to α-quinol, the interaction energies of the enclosed molecules with the cage can be evaluated. The heat of the transition also provides information about the relative stabilities of the α- and the β-form of quinol. The measurements on the clathrate compounds themselves will be published shortly.

For the present measurements a twin calorimeter has been constructed which can be used to determine heats of solution or reaction of a wide range of substances. The solutions are in contact with glass surfaces only, so that corrosive or organic solvents can be used freely, and each calorimeter is pressure- and vacuum-tight. The calorimeter can be used for differential measurements, as in this research, in which electrical energy is used to compensate for the difference in the heat of solution of two substances when dissolved one in each calorimeter, or for direct measurements, also using electrical compensation. The maximum sensitivity is such that temperature differences between the two calorimeters of about $1 \times 10^{-6}°$ can be observed. Only very small quantities of solute are therefore required.

Experimental

Calorimeter.—The twin calorimeter (Fig. 1) consists of two similar Dewar vessels, supported from a flat brass plate in such a way that the joints between the plate and calorimeters are vacuum- and pressure-tight. Each calorimeter has inside it a stirrer, a sample-bulb holder and breaker, a calibrated electric heater, and two thermels. These project into the calorimeters from the top plate through vacuum- and pressure-tight seals. The whole assembly is immersed in a thermostat held at $25{\cdot}00° \pm 0{\cdot}003°$.

Dewar Vessels.—The calorimeters, *A*, *A'*, have a capacity of 500 c.c. and are made as nearly identical as possible. The top of each Dewar vessel is flanged and ground to a flat surface. Rubber gaskets are cemented to the flanges and also to the brass plate with Bostik cement. Each calorimeter is supported from the bottom by means of a cork cup, *C*, glued to a brass plate. This slides over tapped brass rods, *B*, projecting down from the top plate, and with the aid of thumb-screws enables the calorimeter to be pressed tightly into position. The heat capacities of the calorimeters when filled with the normal charge of about 300 c.c. of water differ by 0·15%, and a correction for this is accordingly applied. The difference in the heat capacities was determined by passing a known amount of electrical energy through the heaters wired in series. The small temperature difference between the two calorimeters was then reduced to zero by applying more heat through the appropriate heater. Errors due to this small difference in heat capacities could also be virtually eliminated by repeating each measurement in alternate calorimeters.

Bulb Holders and Breakers.—The samples are sealed into thin-walled glass bulbs, *R*, about 2 cm. in diameter, after the latter has been filled with dry air. The sample bulb rests on a glass ring, *M*, supported by a glass rod from the top plate. A glass claw, *G*, holds the bulb in place

from above, and prevents it from floating in the surrounding liquid. The claw is at the end of a thin glass tube which is waxed to a stainless-steel rod just below the surface of the top plate. The steel rod passes through a Wilson-type vacuum seal, *W* (Wilson, *Rev. Sci. Instr.*, 1941, **12**, 91), attached to the top plate, and when the rod is depressed, the sample bulb is broken and thrust completely through the supporting ring. This ensures that the solute dissolves as quickly as possible.

Thermels.—There are two thermels, *T*. The main one indicates the temperature difference between the two calorimeters, and the subsidiary one indicates the temperature difference between one of the calorimeters and the surrounding bath. The main thermel consists of 19 chromel–constantan junctions and one copper–constantan junction, the last to avoid external thermal E.M.F.s. The relative diameters of the chromel and constantan wires are chosen to give the maximum ratio of electrical to thermal conductivity, and are 24 and 26 s.w.g., respectively. Since a limiting factor in the design of the thermel is the heat conducted along the wires, it is possible to assign a factor of merit, *m*, to different combinations of thermocouple materials, which is identical with that obtained by Hornig and O'Keefe (*ibid.*, 1947, **18**, 474) for radiation thermocouples. This is given by $m = E/(\sqrt{k_1 r_1} + \sqrt{k_2 r_2})$, where E is the thermoelectric

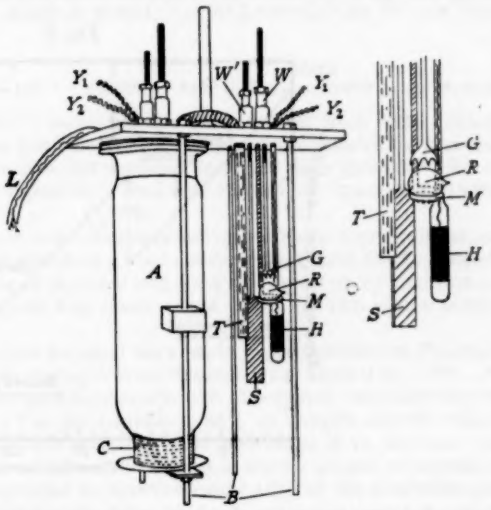


FIG. 1.

A, Dewar vessel.
B, tapped rods.
C, cork support.
G, bulb breaker.
H, heater.
L, output leads.
M, bulb holder.
R, sample bulb.
S, stirrer.
T, thermels.
W and W', "Wilson" seals.
Y_1 and Y_2, current and potential leads.

power of the junction, k_1 and k_2 are the thermal conductivities of the two wires, and r_1 and r_2 are the electrical resistivities. The choice of chromel–constantan junctions was determined by the ready availability of these wires coupled with a relatively high factor of merit, *m*.

The thermel junctions are insulated with Bakelite varnish and embedded in naphthalene at the bottom of the thin glass sheaths. Each junction is pressed tightly against the flat bottom of its sheath. The connecting wires which pass over the top of the brass plate from one calorimeter to the other are insulated from the water by a liberal coating of beeswax–resin mixture. The copper output leads, *L*, are connected through a resistance network to a photoelectric galvanometer amplifier, using negative feedback, similar to the one described by Preston (*J. Sci. Instr.*, 1946, **23**, 173). The resistance network is wired on a wafer switch immersed in oil in a well-lagged metal box. This enables the sensitivity of the detecting system to be varied stepwise by means of series resistances, and also the amplifier can be switched to a manganin resistance equal in value to that of the thermel, in order to check the zero position. All leads were electrically screened by earthed braiding. The sensitivity of the amplifier is normally adjusted so that 1 mm. deflection of the secondary galvanometer corresponds to a temperature difference between the two calorimeters of 4×10^{-4}°.

The subsidiary thermel consists of four chromel–constantan junctions, and is connected to a galvanometer. Its sensitivity is such that 1 mm. deflection of the galvanometer corresponds to a temperature difference between the calorimeter and the bath of 0·001°.

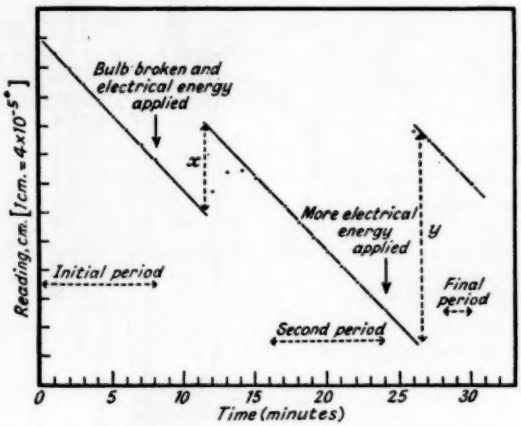
Stirrers.—These are of the paddle type, and consist of similar pieces of sheet Pyrex glass, *S*,

fused to narrow glass tubes. The glass tubes are waxed to stainless-steel rods just below the top plate, and the steel rods pass through Wilson seals, *W'*, lubricated with silicone grease. The stirrers are driven at identical speeds (about 150 r.p.m.) by means of flexible cables connected to either end of a single shaft of a reduction gear driven by a synchronous motor.

Heaters.—The heaters, *H*, of resistance approximately 92 ohms, are wound with 40 s.w.g. Eureka wire on a varnished cylinder of copper foil. The heater coil is wrapped with aluminium foil and coated with Bakelite varnish. Current and potential leads, Y_1, Y_2, are soldered to the coil, and the resistances of the two are adjusted to be the same to within 0·03%. The entire assembly is enclosed tightly in a glass sheath (thickness, *ca.* 0·25 mm.), and the leads pass through a tube which is cemented into a tight-fitting hole in the brass plate. The resistances of the heaters are measured potentiometrically under working conditions, a Tinsley Vernier potentiometer being used. They can also be checked at any time with the current-standardising arrangement.

The amount of electrical energy supplied to the heaters is measured by means of a simple potentiometric arrangement similar to that described by Westrum and Robinson (" Transuranium Elements," Part II, National Nuclear Energy Series). In this arrangement, the current flowing through the heaters and a standard resistance is maintained at a fixed value by balancing

FIG. 2.



the potential drop across the standard resistance against a Weston cell. The heater current can be switched to a dummy load or to either calorimeter, and the time during which the current flows through a calorimeter is measured by a stop-watch reading to 0·02 sec. which is mechanically linked to the switch.

Procedure.—Almost equal amounts of β-quinol and α-quinol (about 90 mg.) are weighed into thin-walled glass bulbs, which are sealed off in a dry atmosphere and mounted in the holders. Equal volumes of solvent at about the correct temperature are run into each Dewar flask, from a constant-volume pipette, and the calorimeters are screwed tightly into place. The whole assembly is mounted in the thermostat, and the calorimeters are brought to the same temperature as the bath to within about 0·005°, the subsidiary thermel and the calorimeter heaters being used. The calorimeters are then allowed to reach equilibrium, and a linear drift in the temperature difference between them is obtained: this usually takes about 0·5 hour. This drift, which is largely due to inequalities in the heats of stirring, is usually between 10 and 25 $\times$ 10^{-6}° per minute. The sample bulbs are then broken simultaneously, and a known amount of electrical energy supplied to compensate for the temperature difference set up. When both samples have dissolved completely, the new reading of the main thermel is plotted for several minutes. A further known amount of electrical energy is then supplied, and a third set of thermel readings taken. A typical graph is shown in Fig. 2. If Q_1 and Q_2 are the respective amounts of heat supplied, then the difference, Q, in the heat changes in the two calorimeters, is given by $Q = Q_1 + (x/y)Q_2$. If both Dewar vessels change in temperature by only small amounts as in these experiments, the initial and final slopes of the temperature–time graph are almost

equal, and there is no difficulty in extrapolation. If the temperature changes are much larger, then the initial and final slopes are appreciably different, owing to the slightly different heat losses of the two Dewar vessels. A correction may then be applied by extrapolating the final slope to a point corresponding to the start of the reaction. This involves the assumption that the bulk of the sample dissolves rapidly, as was in fact the case in all these experiments. The errors introduced are very small unless the time of solution is particularly long. This procedure also eliminates errors which might be caused owing to changes in the heat of stirring brought about by the breaking of the bulbs. Corrections which arise from the fact that the two Dewar vessels are not kept at exactly the same temperature whilst the samples are dissolving, can be shown to be less than 0·1% of the heat of solution from a knowledge of the observed temperature differences, and the thermal leakage coefficients of the calorimeters (approx. 0·001°/min./degree). A correction for the heat of breaking a bulb is unnecessary, as bulbs of closely similar volumes are always used. The heat of breaking an empty bulb filled with dry air is about −0·05 cal. ($1·7 \times 10^{-4}$°). This absorption of heat is largely due to the expansion of water vapour into the dry air.

Heat of Solution of Potassium Chloride.—In order to test the accuracy and reproducibility of the calorimeter, the heat of solution of potassium chloride in water has been measured. The results obtained for the reaction KCl (solid) + $6000H_2O$ = KCl,$6000H_2O$ at 25° are shown below:

Run no.	1	2	3	4	Mean
ΔH, cal.	+4159	+4162	+4157	+4158	4159 ± 3 cal. = 17,400 ± 10 abs. joules

The potassium chloride was an " AnalaR " sample, twice recrystallised from water, dried in an oven, and finally heated for some time just below the melting point to remove the last traces of water. The value of this heat of solution, interpolated from the data given in " Selected Values of Chemical Thermodynamic Properties," National Bureau of Standards, 1950, is +4151 cal.

Preparation of Quinol Samples.—*α-Quinol.* Commercial quinol was recrystallised once from water and once from ethyl alcohol, dried in a vacuum-desiccator, and finally heated at 150° for some time to ensure the absence of β-quinol and solvent. Analysis by titration with ceric sulphate solution (Kolthoff and Lee, *Ind. Eng. Chem., Anal.*, 1946, **18**, 452) gave a purity of 99·9—100·0%.

β-Quinol. The first attempts to prepare β-quinol were made by the method of Powell and Riesz (personal communication), in which quinol is recrystallised from alcohol at −78°. The samples obtained gave *X*-ray powder photographs characteristic of β-quinol, but when they were dissolved in water, a gas was evolved. The gas contained 28% of oxygen and the rest was apparently nitrogen. It seems likely, therefore, that this substance is in fact an " air " clathrate compound. The total volume of gas evolved from a known weight of sample was measured with a nitrometer, and corresponded to approximately 12% of the available spaces filled in the β-quinol lattice.

It was found that β-quinol, free from enclosed gases, can be conveniently prepared by recrystallisation from ethyl alcohol under controlled conditions. A solution of quinol in ethyl alcohol is boiled for some time to remove air and α-quinol nuclei, and the container tightly stoppered. β-Quinol crystallises out on cooling. Ethyl alcohol seems to be specific for this purpose, since water, *n*-propyl alcohol, *n*-butyl alcohol, and ether under similar conditions all give α-quinol. Several calorimetric measurements were carried out on samples prepared in this way, but on analysis the β-quinol was found to contain 0·7—0·9% of ethyl alcohol, which was tenaciously retained, even under rotary-pump vacuum for prolonged periods. It is possible that, although the ethyl alcohol molecule is too large to form a normal clathrate compound, yet small amounts can be accommodated in the β-quinol lattice.

Almost pure β-quinol (99·8% with respect to ceric sulphate) was finally prepared by recrystallisation of quinol from air-free *n*-propyl alcohol in the presence of a seed of argon clathrate compound. The crystals deposited were filtered off, and dried in a vacuum-desiccator. Since β-quinol tends to change into α-quinol when kept, the calorimetric measurements were made on fresh samples. Frequent density checks were made on portions of the sample both before and after measurement, since α- and β-quinol can be distinguished readily by determining their densities (1·33 for α-, 1·26 for β-) by flotation. However, the pure samples of β-quinol appear to be much more stable than those obtained from ethyl alcohol.

Results.—Five different samples of β-quinol were used; the first three were prepared from ethyl alcohol, and the other two from *n*-propyl alcohol. The former samples retained appreci-

able amounts of solvent, and the values obtained are therefore too high. A correction can be made for this, and the corrected values are given in the last column of the table. The correction can only be approximate, however, as the actual state of the retained alcohol is uncertain.

Heat of transformation of α- into β-quinol.

Sample	Purity, %, by titration	ΔH, kcal./mole	ΔH, corr. for retained alcohol	Sample	Purity, %, by titration	ΔH, kcal./mole
A	—	$0{\cdot}21_0$	—	Samples from *n*-propyl alcohol:		
B	99·1	$0{\cdot}22_9$	0·13	D	99·8	$0{\cdot}13_9$
B	99·1	$0{\cdot}23_8$		E	99·8	$0{\cdot}12_8$
C	99·3	$0{\cdot}19_6$	0·12	E	99·8	$0{\cdot}11_4$
Average corrected value $0{\cdot}12_5$				Average value of ΔH = 0·13 kcal./mole = $0{\cdot}5_4$ abs. kjoule/mole		

(The heat of solution of α-quinol at these concentrations is 4·7 kcal./mole.)

The trace of impurity still remaining in the β-quinol in samples D and E will probably cause the values obtained to be too high, whilst small amounts of α-quinol, if present, will act in the opposite direction. These effects are unlikely to be greater than 0·02 kcal., and hence we may write α-quino (solid) ⇌ β-quinol (solid): $\Delta H = 0{\cdot}13 \pm 0{\cdot}03$ kcal./mole = $0{\cdot}5_4 \pm 0{\cdot}1_2$ abs. kjoule/mole.

Discussion.—Since β-quinol is less stable thermochemically than α-quinol, the latter will be the stable modification at low temperatures if the two forms are enantiotropic (Robertson and Ubbelohde, *Proc. Roy. Soc.*, 1938, *A*, **167**, 122). However, α-quinol also seems to be stable up to its m. p., since samples of β-quinol go over rapidly into α-quinol at high temperatures, and hence the system α–β-quinol is probably monotropic.

The very small energy difference between the two forms of quinol may be explained by the more extensive hydrogen bonding in the β-form, which almost compensates for the energy lost by the fewer van der Waals contacts. A rather similar situation is found in the system α–β-resorcinol (Robertson and Ubbelohde, *loc. cit.*).

[*Added in proof*, 8.9.52.] Since this paper was submitted, an abstract has appeared of work by Nitta, Séki, Chihara, and Suzuki on the vapour pressures of crystalline intermolecular compounds (*Chem. Abs.*, 1952, **46**, 3820; *Sci. Papers Osaka Univ.*, No. 29), and further details have been kindly sent to us by Professor Séki. From vapour-pressure measurements on samples of quinol, these workers deduce a value for $\Delta H_{\alpha-\beta\text{-quinol}}$ of $-1{\cdot}58 \pm 0{\cdot}30$ kcal./mole, in marked disagreement with our value of $+0{\cdot}13 \pm 0{\cdot}03$ kcal./mole. Nitta *et al.* claim to have prepared β-quinol by heating the methyl alcohol clathrate compound at 60° for about half a day in a high vacuum, but no analysis of the sample was made. We have attempted to repeat this preparation by heating some methyl alcohol clathrate compound at 60° for 20 hours under a "black" vacuum. On titration with ceric sulphate solution, the original sample contained 91·7% of quinol, corresponding to $3C_6H_4(OH)_2{\cdot}0{\cdot}93MeOH$, and the product after heat treatment contained 93·2% of quinol. This indicates that only about 0·2 mol. of the original methyl alcohol had been removed. Flotation experiments also indicate the absence of appreciable amounts of β-quinol. The *X*-ray powder photographs of the methyl alcohol clathrate compound would, of course, be similar to that of β-quinol.

It seems likely therefore, that Nitta *et al.* were not working with pure samples of β-quinol

We are grateful to Mr. H. M. Powell for taking *X*-ray powder photographs of the samples of β-quinol. One of us (D. F. E.) is also indebted to the Department of Scientific and Industrial Research for a maintenance grant.

PHYSICAL CHEMISTRY LABORATORY, SOUTH PARKS ROAD, OXFORD. [*Received, May 15th*, 1952.]

755. *Amino-acids and Peptides. Part IX.* γ-L-Glutamyl-L-alanine, -L-valine, and -L-leucine.*

By D. A. Rowlands and G. T. Young.

The above-named dipeptides have been synthesised by the γ-azide route, and their autohydrolysis has been investigated by partition chromatography.

The discovery by Hanes, Hird, and Isherwood (*Nature*, 1950, **166**, 288; *Biochem. J.*, 1952, **51**, 25) of the enzymic transpeptidation of γ-glutamyl-peptides has lent added interest to the chemical investigation of these compounds. The enzymic reaction has indeed certain similarities to the transamidation which has been observed on heating aqueous solutions of γ-glutamyl-peptides, resulting in the formation of 5-ketopyrrolidine-2-carboxylic acid with consequent hydrolysis of the peptide bond (Le Quesne and Young, *J.*, 1952, 594); the latter reaction is the intramolecular counterpart of the intermolecular enzymic transpeptidation.

Continuing our study of such compounds, we have synthesised the γ-L-glutamyl derivatives of L-alanine, L-valine, and L-leucine. We have used the γ-azide route developed by Hegedüs (*Helv. Chim. Acta*, 1948, **31**, 737), by ourselves (*Nature*, 1949, **163**, 604; Part II, *J.*, 1950, 1959), and by Šorm and Rudinger (*Coll. Czech. Chem. Comm.*, 1950, **15**, 491).

Some difficulty has been reported (*e.g.*, Coleman, *J.*, 1950, 3223) with larger-scale preparations of γ-ethyl L-glutamate hydrochloride; we have obtained consistently good yields by increasing the proportion of ethanol and keeping the temperature below 30° throughout the experiment. L-Alanine ethyl ester hydrochloride, first prepared by Curtius and Koch (*J. pr. Chem.*, 1888, [ii], **38**, 487) with melting point 64—68°, has been made by Synge's low-temperature esterification procedure (*Biochem. J.*, 1948, **42**, 99), giving a material melting at 76°. We have also obtained L-valine methyl ester hydrochloride with melting point and optical rotation considerably higher than previously reported (Synge, *loc. cit.*). It will, however, be noted that our γ-L-glutamyl-L-valine has no observable rotation in aqueous and in acid solution; nevertheless, hydrolysis gave a solution with a rotation greater than would be possible if either one of the component amino-acids were racemised and, in view of the optical purity of the starting materials and the known route of synthesis, we believe our product to be as named.

γ-L-Glutamyl-L-alanine undergoes autohydrolysis in the normal manner, yielding alanine but little glutamic acid. We have taken advantage of the favourable differences in R_F values in partition chromatography of the products, to show that the rate of formation of alanine is closely paralleled by the formation of 5-ketopyrrolidine-2-carboxylic acid. The valine and leucine analogues, as would be expected, are much more resistant to hydrolysis.

Hamilton (*J. Biol. Chem.*, 1945, **158**, 375) has shown that the rate of ring closure of glutamine is greater in a phosphate buffer than in an acetate buffer of the same pH. By means of paper partition chromatography, we have followed the progress of the autohydrolysis of γ-L-glutamyl-glycine and -L-alanine in acetate and phosphate buffers; visual comparison of the intensities of the spots corresponding in position to glycine and alanine respectively suggests that these amino-acids may be formed a little more rapidly in the presence of phosphate, but quantitative determinations are required to confirm this conclusion.

Experimental

M. p.s are uncorrected. Combustion analyses are by Drs. Weiler and Strauss.

γ-Ethyl L-Glutamate Hydrochloride (*Modified Procedure*).—L-Glutamic acid (50 g.) was suspended in ethanol (1 l.), and dry hydrogen chloride passed in, the temperature being kept below 30°. After 45 minutes the clear solution was evaporated to dryness under reduced pressure and the product reprecipitated from ethanol by ether, giving γ-ethyl L-glutamate hydrochloride, m. p. 132—135° (59·4 g., 82%).

* Part VIII, *J.*, 1952, 1574.

L-Alanine Ethyl Ester Hydrochloride.—L-Alanine (10 g.), dissolved in N-ethanolic hydrogen chloride (200 ml.), was set aside at room temperature for 24 hours. After evaporation to dryness at reduced pressure the process was twice repeated and the remaining syrup induced to crystallise by repeated evaporation with ethanol. Recrystallisation from ethanol–ether gave L-alanine ethyl ester hydrochloride (15 g., 88%) as deliquescent crystals, m. p. 76°, $[\alpha]_D^{19}$ +3·1° (*c*, 2·5 in water) (Found: C, 38·8; H, 7·8; N, 9·3; Cl, 23·3. Calc. for $C_5H_{12}O_2NCl$: C, 39·1; H, 7·9; N, 9·1; Cl, 23·1%).

Carbobenzyloxy-γ-L-glutamyl-L-alanine Ethyl Ester.—Carbobenzyloxy-γ-L-glutamylhydrazide (Part II, *loc. cit.*; 3·6 g.) was dissolved in water containing concentrated hydrochloric acid (4 ml.), chloroform (50 ml.) was added, and the mixture stirred at 0° while sodium nitrite (1·2 g.) in water (10 ml.) was gradually added. After being washed with water and dried (Na_2SO_4) for a few seconds, the chloroform solution of the azide was added to a solution of L-alanine ethyl ester (3 g.; liberated from the hydrochloride by the calculated amount of ammonia in chloroform) in chloroform (5 ml.) at 0°. The mixture was kept for several hours in ice and overnight at room temperature, washed with dilute hydrochloric acid and then water, dried (Na_2SO_4), and evaporated under reduced pressure. The product solidified under light petroleum and was crystallised from ethyl acetate–light petroleum, giving *carbobenzyloxy-γ-L-glutamyl-L-alanine ethyl ester*, m. p. 108—111° (2·2 g., 47%) raised by recrystallisation to 112—113° (Found: C, 57·0; H, 6·3; N, 7·4. $C_{18}H_{24}O_7N_2$ requires C, 56·8; H, 6·4; N, 7·4%).

Carbobenzyloxy-γ-L-glutamyl-L-alanine.—The above ester (1·7 g.) was dissolved in N-sodium hydroxide (15 ml.) and kept at room temperature for 2 hours. After acidification with 5N-hydrochloric acid the solution was extracted with ethyl acetate (4 × 30 ml.), and the combined extracts were washed with a little water, dried (Na_2SO_4), and evaporated under reduced pressure. The remaining *carbobenzyloxy-γ-L-glutamyl-L-alanine* (1·5 g., 95%) was recrystallised from acetone–ether; it then had m. p. 150—154° (Found: C, 54·9; H, 5·6; N, 8·2. $C_{16}H_{20}O_7N_2$ requires C, 54·6; H, 5·7; N, 8·0%).

γ-L-Glutamyl-L-alanine.—Carbobenzyloxy-γ-L-glutamyl-L-alanine (0·5 g.) in aqueous methanol (20 ml.) was hydrogenated in the normal manner in the presence of palladium black. The filtrate was evaporated to dryness and the product recrystallised from aqueous ethanol, giving *γ-L-glutamyl-L-alanine* (0·29 g., 94%), m. p. 185—187° (Found: C, 43·8; H, 6·6; N, 13·1. $C_8H_{14}O_5N_2$ requires C, 44·0; H, 6·5; N, 12·8%), $[\alpha]_D^{18}$ −22·1° (*c*, 5·0 in water); R_F: in *n*-butanol, 0·02; in phenol, 0·33.

L-Valine Methyl Ester Hydrochloride.—Esterification of L-valine (11·2 g.) was effected with N-methanolic hydrogen chloride as described by Synge (*loc. cit.*). After reprecipitation from methanol by ether, the hydrochloride (13·1 g., 85%) had m. p. 125—135°, raised to 161—162° by recrystallisation from acetone, $[\alpha]_D^{20}$ +15·6° (*c*, 3·8 in water) (Found: C, 43·0; H, 8·5; N, 8·8; Cl, 21·2. Calc. for $C_6H_{14}O_2NCl$: C, 42·7; H, 8·3; N, 8·3; Cl, 21·6%).

Carbobenzyloxy-γ-L-glutamyl-L-valine.—Carbobenzyloxy-γ-L-glutamylhydrazide (5 g.) was converted into the azide and coupled with L-valine methyl ester (4·4 g.) in chloroform as described for the alanine analogue. After the final evaporation of the chloroform, carbobenzyloxy-γ-L-glutamyl-L-valine methyl ester (4·3 g., 64%) remained as a syrup which could not be induced to crystallise; a portion (1·15 g.) was hydrolysed in the usual manner, giving *carbobenzyloxy-γ-L-glutamyl-L-valine* (0·95 g., 86%) as a syrup, which was dissolved in N-sodium carbonate and precipitated by acid; the oil crystallised after several months. Recrystallisation from ethyl acetate–light petroleum raised the m. p. from 148—155° to 153—156° (Found: C, 57·3; H, 6·5; N, 7·2. $C_{18}H_{24}O_7N_2$ requires C, 56·8; H, 6·4; N, 7·4%).

γ-L-Glutamyl-L-valine.—Carbobenzyloxy-γ-L-glutamyl-L-valine (0·34 g.) was hydrogenated in the normal manner. After reprecipitation from water with acetone the *γ-L-glutamyl-L-valine* (0·2 g., 90%) had m. p. 207° (Found: C, 48·3; H, 7·2; N, 11·7. $C_{10}H_{18}O_5N_2$ requires C, 48·7; H, 7·4; N, 11·4%), $[\alpha]_D^{19}$ 0·0° ± 0·5° (*c*, 2·4 in water); a similar value was observed in N-hydrochloric acid (*c*, 2·1). Hydrolysis gave a solution with a rotation higher than could be accounted for by L-glutamic acid or L-valine alone. R_F: in *n*-butanol, 0·01; in phenol, 0·45.

Carbobenzyloxy-γ-L-glutamyl-L-leucine.—Carbobenzyloxy-γ-L-glutamylhydrazide (5 g.) was converted into the azide and coupled with L-leucine methyl ester (11·5 g., from 14·8 g. of L-leucine methyl ester hydrochloride, m. p. 148—149°) in chloroform solution as above. Carbobenzyloxy-γ-L-glutamyl-L-leucine methyl ester (5·4 g., 78%) was obtained as a syrup. A portion (1·7 g.) was hydrolysed in the usual manner, giving *carbobenzyloxy-γ-L-glutamyl-L-leucine* (1·5 g., 91%) as a syrup which crystallised after precipitation from sodium carbonate solution and storage for several months; it had m. p. 83—85°. Recrystallisation from ethyl acetate–light petroleum gave a second crystalline form, m. p. 132—134° (Found: C, 57·9; H,

6·8; N, 6·8. $C_{19}H_{26}O_7N_2$ requires C, 57·9; H, 6·7; N, 7·1%). In the final crystallisation a second crop was obtained, m. p. 85—90°, which could be converted into the higher-melting form by seeding at the m. p.

γ-L-Glutamyl-L-leucine.—Carbobenzyloxy-γ-L-glutamyl-L-leucine (0·24 g.) was hydrogenated in the usual manner. After precipitation from water with acetone, the *γ-L-glutamyl-L-leucine* (0·12 g., 76%) had m. p. 185° (Found: C, 50·3; H, 7·7; N, 11·1. $C_{11}H_{20}O_5N_2$ requires C, 50·8; H, 7·7; N, 10·8%), $[\alpha]_D^{19}$ −13·5° (*c*, 2·3 in water); R_F: in *n*-butanol, 0·03; in phenol, 0·56.

Autohydrolysis of γ-L-Glutamyl-L-alanine.—Solutions (1%) of γ-L-glutamyl-L-alanine in water and in 0·5N-hydrochloric acid were heated in sealed tubes at 100°. At intervals tubes were removed and their contents examined by paper partition chromatography, phenol saturated with water being the mobile phase; controlled quantities of each solution were placed on the chromatogram by means of a graduated capillary tube. The chromatograms were developed in the normal manner with ninhydrin. The following relative intensities were evaluated visually:

Time (hrs.)	Aqueous solution			0·5N-Acid solution		
	Dipeptide	Glutamic acid	Alanine	Dipeptide	Glutamic acid	Alanine
0	+ + + +	—	—	+ + + +	—	—
1·5	+ + +	±	+	+ +	+ + +	+ + +
3	+ +	±	+ +	+	+ + +	+ + +
8	+	±	+ + +	−	+ + +	+ + + +
24	±	±	+ + + +	−	+ + +	+ + + +

Autohydrolysis of γ-L-Glutamyl-L-valine and -L-leucine.—Similar experiments with aqueous solutions (1%) of γ-L-glutamyl-L-valine and -L-leucine gave the following results:

Time (hrs.)	γ-L-Glutamyl-L-valine			γ-L-Glutamyl-L-leucine		
	Dipeptide	Glutamic acid	Valine	Dipeptide	Glutamic acid	Leucine
0	+ + + +	—	—	+ + + +	—	—
1	+ + +	—	±	+ + + +	—	±
4	+ + +	—	±	+ + +	—	±
10	+ + +	—	+	+ + +	—	+
24	+ + +	±	+ +	+ + +	±	+

After a total of 96 hours at 100° the intensities for the second amino-acid were: L-valine, + + + +; L-leucine, + + + +.

Effect of Buffer Solutions.—For γ-L-glutamyl-L-alanine and -glycine, hydrolyses were carried out in both acetate and phosphate buffers (pH 6·0; 0·05M).

Time (hrs.)	Acetate buffer			Phosphate buffer		
	γ-L-Glutamyl-L-alanine	Glutamic acid	Alanine	γ-L-Glutamyl-L-alanine	Glutamic acid	Alanine
0	+ + + +	—	—	+ + + +	—	—
1	+ + +	—	+	+ + + +	—	+
2	+ + +	—	+	+ + +	—	+ +
4	+ +	—	+ + +	+ +	±	+ + +
7	+	—	+ + +	+	±	+ + + +
12	+	—	+ + +	±	±	+ + + +
24	—	—	+ + + +	—	±	+ + + +
	γ-L-Glutamyl-glycine	Glutamic acid	Glycine	γ-L-Glutamyl-glycine	Glutamic acid	Glycine
0	+ + + +	?	—	+ + + +	?	—
0·5	+ + + +	?	±	+ + + +	?	+
1·5	+ + + +	?	±	+ + +	?	+ +
6	+ + +	?	+ + +	+ +	?	+ + + +
12	+ +	?	+ + + +	+	?	+ + + +
24	+	?	+ + + +	±	?	+ + + +

The poor separation of this dipeptide from glutamic acid makes the detection of the latter difficult.

Detection of 5-Ketopyrrolidine-2-caboxylic Acid during the Autohydrolysis of γ-L-Glutamyl-L-alanine.—By using more concentrated (10%) solutions of γ-L-glutamyl-L-alanine and employing butanol (acid-free and redistilled) saturated with water as the mobile phase, the progressive formation of 5-ketopyrrolidine-2-carboxylic acid during aqueous hydrolysis was observed by spraying the dried chromatogram with a solution of methyl-orange (saturated, in ethanol–ethyl

acetate, 1 : 1); in the results below, the figures in parentheses indicate R_F values. In parallel experiments in which the chromatograms were sprayed with methyl-red, differentiation between the acid and the dipeptide was less clear and the greater sensitivity of the indicator revealed considerable tailing; control experiments, however, indicate that this is a function of the concentration; the figures in the second table therefore represent the maximum R_F values of the spots observed and may be regarded as an indication of the concentration of the 5-keto-pyrrolidine-2-carboxylic acid.

	Methyl-orange		Methyl-red
Time (hrs.)	Dipeptide	5-Ketopyrrolidine-2-carboxylic acid	5-Ketopyrrolidine-2-carboxylic acid
0	+ + + (0·08)	—	—
0·5	+ + (0·08)	—	+ (0·25)
1	+ + (0·08)	—	+ (0·37)
1·5	+ (0·08)	—	+ (0·45)
3	± (0·08)	+ (0·5)	+ (0·53)
6	—	+ + (0·5)	+ (0·57)
12	—	+ + (0·5)	+ (0·60)
24	—	+ + + (0·5)	+ (0·64)

Comparison with the earlier table showing the formation of alanine under similar conditions confirms the suggestion that both products are formed simultaneously.

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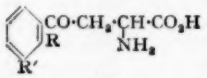
756. *The Optical Resolution of Aromatic Amino-acids on Paper Chromatograms.*

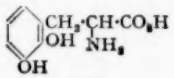
By C. E. DALGLIESH.

It has been found that many racemic aromatic amino-acids can be resolved into their optical enantiomorphs on paper chromatograms. Sufficient cases have been examined to enable a preliminary formulation to be made of the structural features necessary for resolution to occur.

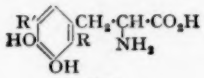
THE optical resolution of amino-acids on paper chromatograms was first reported in 1951 by Kotake, Sakan, Nakamura, and Senoh (*J. Amer. Chem. Soc.*, 1951, **73**, 2973). In a recent paper (Dalgliesh, *J.*, 1942, 137) it was shown that DL-kynurenine (I; R = NH_2, R′ = H) is resolved into its optical enantiomorphs, a result confirmed by Mason and Berg (*J. Biol. Chem.*, 1952, **195**, 515). Similar resolution has also been found to occur with 3-hydroxy-DL-kynurenine (I; R = NH_2, R′ = OH) (Dalgliesh, *Biochem. J.*, 1952, **52**, 3).



(I)



(II)



(III)

While investigating aspects of tyrosine metabolism the resolution of 2 : 5-dihydroxyphenyl-DL-alanine was observed, and other related amino-acids have therefore been investigated.

Resolution has also been found with 2 : 3-dihydroxyphenyl-DL-alanine (II) and 3 : 4-dihydroxy-2-methylphenyl-DL-alanine (III; R = Me, R′ = H), whereas none occurred with 3 : 4-dihydroxyphenyl-DL-alanine (III; R = R′ = H) or its 5-methyl derivative (III; R = H, R′ = Me). Resolution was shown by the appearance of two spots on the chromatogram of a chemically pure racemate, these being of equal size, shade, and intensity by whatever means they were revealed. Where optical isomers were available, these gave only a single spot which corresponded to one of the spots given by the racemate: thus, both D- and L-isomers of 2 : 5-dihydroxyphenylalanine (Neuberger, *Biochem. J.*, 1948, **43**, 599) gave spots corresponding to the two spots given by the racemate, and the ratio of the R_F values of the authentic D- and L-compounds was the same as that for the two spots given by the racemate.

If paper chromatography were to involve purely partition phenomena, as is assumed in, *e.g.*, the initial theory of Consden, Gordon, and Martin (*Biochem. J.*, 1944, **38**, 224) no resolution of a racemate could occur from optically inactive solvents. However, observed R_F values do not always agree with values calculated from partition coefficients, and other factors must therefore be involved. One of the more important of these is adsorption, and a higher degree of adsorption of one optical isomer of a racemic solute on the surface of the optically active cellulose would lead to resolution. Cellulose consists of long flat molecules, packed in sheets and containing large numbers of groups forming hydrogen bonds. Adsorption would therefore be most likely with substances containing flat areas, such as an aromatic ring, and hydrogen-bonding groups, such as the α-amino-acid grouping. That it does occur is well shown in the case of tryptophan which, when run on a paper chromatogram with pure water as solvent, does not move with the solvent front, but shows an R_F value of 0·6—0·7 (Synge and Tiselius, *Acta Chem. Scand.*, 1949, **3**, 231). No evidence has been reported of the resolution on chromatograms of racemic tryptophan, and it must therefore be assumed that the degrees of adsorption of the D- and the L-form on the cellulose surface are similar. It is, however, reasonable to suppose that other racemic substances might fit the molecular architecture of the cellulose surface more closely in one of the optically active forms, and this is considered to be the explanation of the resolution observed in the cases described here.

In all the cases in which resolution has been observed (see above), the ratio of the R_F values of the two optical isomers is about 0·9, and this suggests that a common mechanism is operative in all cases. With 2 : 5-dihydroxyphenylalanine the D-isomer is the faster, so that the L-isomer is more strongly adsorbed. By analogy it can be provisionally assumed that the D-isomer is the faster for the other phenylalanine derivatives which show resolution, though it is hoped to obtain more definite evidence on this point in the future by using D- and L-amino-acid oxidases. In the case of the kynurenines (I; R = NH_2, R′ = H or OH) the faster-running isomer corresponds to the naturally occurring L-isomer (Dalgliesh, *locc. cit.*), and the D-isomers must in these cases be more strongly adsorbed. The side-chain of the kynurenines contains one more carbon atom (in the form of a carbonyl group attached to, and therefore coplanar with, the benzene ring) than that of phenylalanine derivatives and the flat (aromatic) area of the molecule therefore bears a different spatial relation to the asymmetric centre, so that a difference between the phenylalanine and kynurenine series is not unreasonable.

In the present work no indication of resolution was observed with 3 : 4-dihydroxyphenyl-DL-alanine or its 5-methyl derivative. No evidence has been reported for the resolution of racemic phenylalanine or tyrosine, and previous work (Dalgliesh, *loc. cit.*) has shown that no resolution occurs with *o*-nitrophenacylglycine, phenacylglycine, or with kynurenine acylated on either the aliphatic or the aromatic amino-group. It is thus possible to formulate tentatively the structural features necessary for resolution: (1) The α-amino-group (and probably also the carboxyl group) should be intact. If both these groups were unable to become simultaneously attached to the cellulose surface, presumably by hydrogen-bonding, resolution would be unlikely, as a "three-point" attachment of the molecular is required for stereochemical specificity. (2) To give this "three-point" attachment the molecule must contain some other portion, such as an aromatic ring, which is also adsorbed on the cellulose surface. Further work is necessary to show to what extent the distance between the two adsorbing centres (aromatic ring and α-amino-acid grouping) is critical, and what degree of configurational rigidity is necessary in the intervening chain. (3) The ring must carry one or more substituents allowing a closer "fit" with the cellulose surface, and hence greater adsorption, with one of the optical isomers than with the other. It is considered likely from the present work that any phenylalanine containing a small substituent in the *ortho*-position may be resolvable on cellulose chromatograms, and that resolution would be due to steric interference of the *ortho*-substituent with some element in the cellulose surface which prevents the D- from being so strongly adsorbed as the L-isomer. (4) Although the cases showing resolution all contain hydrogen-bonding groups on the benzene ring there is no evidence as yet to show whether these groups are essential for resolution.

If these assumptions are correct and if hydrogen-bonding groups on the aromatic ring are unnecessary, it is possible that *o*-tolyl-DL-alanine and *o*-chlorophenyl-DL-alanine, for example, should be optically resolvable on paper chromatograms, whereas the corresponding *m*- and *p*-isomers, or a substance such as α-naphthylalanine (cf. tryptophan) would not. Optical resolution might also occur with, say, substituted phenyl-lactic acids. It is hoped to extend this investigation to other aromatic amino-acids. The method is obviously of potential value for preparative resolutions on columns of cellulose or other optically active materials.

Experimental

Amino-acids.—2 : 5-Dihydroxy-DL, -D-, and -L-alanine were supplied by Dr. A. Neuberger; racemic 2 : 3-dihydroxy-, 3 : 4-dihydroxy-2-methyl, and 3 : 4-dihydroxy-5-methylphenylalanine were supplied by Mr. J. Harley-Mason (cf. Cromartie and Harley-Mason, *J.*, 1952, 1052); 3 : 4-dihydroxyphenylalanine was commercial material.

Chromatography.—This was carried out by the descending technique on strips, 30" in length, of Whatman No. 4 paper. Racemates which were resolved showed, after travelling a short distance, an elongaged spot which as it proceeded down the paper became dumb-bell shaped and finally separated into two spots. It was frequently considered desirable to allow substances to travel about 60 cm. This necessitated allowing the solvent to run off the paper, which was serrated at the lower edge to ensure an even flow. All chromatograms were run with the organic phase of butanol–acetic acid–water mixtures. It was found that variation in the composition of the mixture did not alter the order in which substances moved, but did alter the rate of travel. The composition was therefore varied, usually by reduction of the acetic acid component, to give mixtures which caused the amino-acid to travel the required distance during a given time (usually 40 hours). As R_F values could not be directly measured tyrosine was used as a reference substance and was given the R_F value 0·4 which it shows in the standard 4 : 1 : 5 butanol–acetic acid–water system of Partridge (*Nature*, 1946, **158**, 270). The values so obtained, being derived from solvents of varying composition, are not strictly comparable but give an approximate idea of the true R_F. They are therefore recorded in the Table as "apparent" mean R_F values (where resolution has occurred the mean value for the two spots is taken). Of greater significance than the R_F values, in the cases of those amino-acids showing resolution, is the ratio of the R_F values of the two resolved components. This is included in the Table, together with the number of determinations on which the value is based.

R_F values.

Phenylalanine derivative	"Apparent" mean R_F Average	Range	Ratio of R_F values of optical isomers Observed	No. of determinations
2 : 5-Dihydroxy	0·32	0·28—0·35	0·89 *	14
2 : 3- ,, ...	0·32	0·26—0·35	0·91	7
3 : 4-Dihydroxy-2-methyl	0·29	0·22—0·34	0·89	8
3 : 4-Dihydroxy	0·25	0·18—0·29	—	—
3 : 4-Dihydroxy-5-methyl	0·34	0·26—0·39	—	—

* The mean ratio for 12 determinations with authentic 2 : 5-dihydroxyphenyl-D- and -L-alanine was also 0·89.

Detection.—For routine work ninhydrin was used in the usual way. A wide range of other reagents applicable to dihydroxyphenyl derivatives was also examined with results reported in the succeeding paper.

I thank Dr. A. Neuberger, F.R.S., and Mr. J. Harley-Mason, whose gifts of amino-acids made this investigation possible.

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757. *The Detection and Differentiation of 3 : 4- and 2 : 5-Dihydroxyphenyl Compounds Related to Tyrosine.*

By C. E. Dalgliesh.

The behaviour of dihydroxyphenyl compounds towards a variety of reagents has been examined. Methods are described by which the 3 : 4- and 2 : 5-dihydroxyphenyl compounds related to tyrosine metabolism can be distinguished.

Two routes for the metabolism of tyrosine lead to dihydroxyphenyl compounds. The action of tyrosinase gives 3 : 4-dihydroxyphenylalanine which is the precursor both of adrenaline-type compounds and of indole derivatives such as adrenochrome. By simple transformations of well-known metabolic occurrence the corresponding 3 : 4-dihydroxyphenyl-ethylamine, -pyruvic acid, and -acetic acid can be derived. The major pathway for tyrosine breakdown, however, has been shown (Knox and LeMay-Knox, *Biochem. J.*, 1951, **49**, 686) to proceed *via* 2 : 5-dihydroxyphenylpyruvic acid and 2 : 5-dihydroxyphenylacetic (homogentisic) acid. The corresponding 2 : 5-dihydroxyphenylacetic acid and 2 : 5-dihydroxyphenylethylamine are therefore of possible occurrence. Both 3 : 4- and 2 : 5-dihydroxyphenyl compounds are strongly reducing and cannot be distinguished by a reagent such as ammoniacal silver nitrate, which in all cases is immediately reduced in the cold. Methods for the differentiation of the 3 : 4- and 2 : 5-dihydroxyphenyl compounds related to tyrosine have therefore been developed, and extended to some analogous compounds.

Previous interest in the detection of dihydroxyphenyl compounds on chromatograms has largely centred on adrenaline and noradrenaline, and James's ferricyanide reagent (James, *Nature*, 1948, **161**, 851; James and Kilbey, *ibid.*, 1950, **166**, 67) has been widely employed with good results (*e.g.*, Hamberg and von Euler, *Acta Chem. Scand.*, 1950, **4**, 1185; Crawford, *Biochem. J.*, 1951, **48**, 203). Although this reagent reacted readily with our compounds, differentiation of the 3 : 4- and the 2 : 5-series was not achieved. The colours obtained are listed in the Table, as are the colours obtained when the treated chromatograms were observed under ultra-violet light which has passed through a Wood's glass filter. Attention was therefore directed to reactions used to detect phenols.

The application of the Folin–Denis reagent (a mixture of phosphomolybdic and phosphotungstic acids) to paper chromatograms has already been described (Cornforth, Dalgliesh, and Neuberger, *Biochem. J.*, 1951, **48**, 598). The reagent has now been found to be much improved by the use of ethanolic ammonia in place of aqueous sodium carbonate for the alkaline spray. The use of phosphomolybdic acid in the estimation of tyrosine metabolites has been developed by Neuberger (*Biochem. J.*, 1947, **41**, 431) and as a detecting reagent in chromatography by Riley (*J. Amer. Chem. Soc.*, 1950, **72**, 5782). Riley concluded that di- and tri-hydric phenols containing *o*- and *p*-hydroxy-groups give immediate blue spots which darken on exposure to ammonia vapour, whereas simple phenols and *m*-polyhydric phenols give no blue colour until after treatment with ammonia. The range of substances tested was small for such wide conclusions. By use of the Folin–Denis reagent, results more useful for the present purpose have been obtained. It has been found that the 2 : 5-compounds all give a blue colour immediately on spraying with the phosphomolybdate–phosphotungstate reagent whereas the 3 : 4-compounds give a marked blue colour only when the paper is made alkaline.

By using only phosphotungstic acid in the reagent, dihydric can be distinguished from monohydric phenols. No colours appear until the paper is made alkaline, whereupon dihydric phenols give spots on a white background, those from the 2 : 5-series being blue and from the 3 : 4-series blue-green. In low concentrations the colours are difficult to distinguish, but the test provides valuable confirmatory evidence. It was long ago shown by Folin (*e.g.*, Folin *et al.*, *J. Biol. Chem.*, 1912, **12**, 239; 1913, **13**, 477) that phosphotungstic acid reacted with dihydric but not monohydric phenols, and the reagent is referred to as Folin's reagent. It also reacts, as is to be expected, with substances such as uric

acid to give blue spots. In the case of the phenolic substances the colour appears rapidly; with uric acid a delay of an hour or hours occurs.

The following abbreviations are used: Dhp = dihydroxyphenyl; Bl = blue; Br = brown; G = green; M = magenta; O = orange; Pk = pink; Pu = purple; Sl = slate-coloured; V = violet; Y = yellow. A dash represents no or negligible colour; p = pale.

		James' ferricyanide		Folin–Denis			Millon's		
	Ninhydrin	visible light	U.V. light	before basification	after basification	Folin's	before heating	after heating	Pauly's
3 : 4-Dhp-alanine	Pu	M	p Pu or Sl	*	Bl	Bl-G	Y	Br	M
3 : 4-Dhp-ethylamine	p Pu	p V	,,	*	Bl	Bl-G	Y	Br	M
3 : 4-Dhp-pyruvic acid	—	p V	,,	p G	Br or Bz-Bl	Bl-G	Y-Br	Br	Br
3 : 4-Dhp-acetic acid	—	p V	,,	*	Bl	Bl-G	Y	Br	Pk
2 : 5-Dhp-alanine	Pu	p V	,,	Bl	Bl	Bl	—	Br	Br-Pk
2 : 5-Dhp-ethylamine	p Pu	p V	,,	Bl	Bl	Bl	—	Br	G
2 : 5-Dhp-pyruvic acid	—	p V	,,	Bl	Bl	Bl	—	Br	G
2 : 5-Dhp-acetic acid	—	p V	,,	Bl	Bl	Bl	—	Br	Br-Pk
2 : 3-Dhp-alanine	Pu	M		*	Bl	G	p Br	Br	O
3 : 4-Dihydroxy-2-methylphenylalanine	Pu	Pk	,,	*	Bl	p Bl	p Y	p Y	M
3 : 4-Dihydroxy-5-methylphenylalanine	Bl-Pu	V	,,	*	Bl	p Bl	p Y	Y	Bl-M
Adrenaline	—	Pk	Y	*	Bl	Bl	p Y	Y-Br	Pk
Noradrenaline	—	M	G	*	Bl	Bl	p Y	Br	Pk

* A pale blue colour may appear before the alkaline spray, but this increases very markedly on basification.

Millon's reaction has been examined both on paper and in the test-tube. On paper satisfactory results have been obtained by using diluted bench reagent. Compounds of the 3 : 4-series give a yellow colour immediately on spraying. When the air-dried paper is heated at 100° for a short while, the 2 : 5-compounds appear as brown spots and the initially yellow spots of the 3 : 4-series also become brown. The procedure renders the paper fragile, but not unduly so. In the test tube Medes's modification (*Biochem. J.*, 1932, **26**, 917) of the method of Folin and Ciocalteau (*J. Biol. Chem.*, 1927, **73**, 627) was used. All the dihydroxyphenyl compounds give copious coloured precipitates when heated with the mercuric sulphate reagent, but give no colour on centrifugation and treatment with nitrite. On the other hand both *N*-methyltyrosine and *p*-hydroxyphenylpyruvic acid behave like tyrosine itself (cf. Neuberger, *loc. cit.*; Knox and LeMay-Knox, *loc. cit.*). Neither 3 : 4- nor 2 : 5-dihydroxyphenyl compounds would therefore interfere with estimations by this procedure.

Pauly's reagent (diazotised sulphanilic acid) was found to give valuable information. The 3 : 4-series, except for the pyruvic acid, all give an immediate pink or magenta colour, whereas the 2 : 5-series give a yellow colour becoming a pinkish-brown or green. These colours can vary under different conditions, and reference compounds should therefore be used.

The Folin–Denis, Folin, and Pauly reagents are all of high sensitivity for the detection of dihydroxyphenyl compounds, and together enable the 3 : 4- and the 2 : 5-series to be differentiated.

Experimental

Chromatography.—Chromatograms were run on Whatman No. 4 paper by the descending technique, with the organic phase of butanol–acetic acid–water mixtures of varying compositions as solvent (cf. preceding paper). 3 : 4- and 2 : 5-Dihydroxyphenylpyruvic acid did not run satisfactorily in this solvent and the results recorded were obtained with spots of a solution applied to filter paper and allowed to dry.

Materials.—3 : 4- and 2 : 5-Dihydroxyphenyl-alanines, -ethylamines, -pyruvic acids, and -acetic acids were supplied by Dr. A. Neuberger, and 2 : 3- and 3 : 4-dihydroxy-2- and -5-methylphenylalanine by Mr. J. Harley-Mason. The adrenaline and noradrenaline were from commercial sources.

Reagents.—(1) *Folin–Denis reagent.* This was used as described by Cornforth *et al.* (*loc. cit.*) with the exception that the alkaline spray was made by mixing 1 volume of aqueous ammonia (*d* 0·88) with 2 volumes of ethanol. This gives rise to very much less background interference than is obtained with a sodium carbonate spray.

(2) *Folin's reagent.* The method for making Folin–Denis reagent described in the Merck Index (fifth edn., Merck, Rahway, N.J., p. 725) was followed, with the omission of phosphomolybdic acid. The resultant reagent had a very pale blue tint in contrast to the pale green of the Folin–Denis reagent. As with the latter it is important to use an all-glass spray. After being sprayed with the reagent and allowed to dry the paper was sprayed with the ethanolic ammonia solution described above.

(3) *Millon's reagent.* For spraying on chromatograms the bench reagent prepared as described in the Merck Index (*op. cit.*, p. 839) was diluted with 2 volumes of water.

(4) *Pauly's reagent.* Diazotised sulphanilic acid was diluted with an equal volume of ethanol before spraying (cf. Evans, Parr, and Evans, *Nature*, **164**, 674) and when dry the chromatograms were made alkaline with the ethanolic ammonia solution described above.

Results.—The colours obtained with the different reagents are summarised in the accompanying Table. For examining chromatograms under ultra-violet light a lamp with a Wood's glass filter was used.

I thank Dr. A. Neuberger, F.R.S., and Mr. J. Harley-Mason for generous gifts of amino-acids and related compounds.

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758. *Experiments on the Synthesis of Carbonyl Compounds. Part VI.* A New General Synthesis of Ketones and β-Keto-esters.*

By R. E. BOWMAN and W. D. FORDHAM.

Esters of tetrahydropyran-2-ol (such as the acetate) undergo thermal decomposition to 2 : 3-dihydropyran and the carboxylic acid under mild conditions. This led to a new and apparently general synthesis of ketones starting from malonic acids and acid chlorides (cf. *Chem. and Ind.*, 1951, 742).

THE main object of the work recorded in this series of papers has been to evolve new methods of synthesis of ketones starting from acid chlorides and substituted malonic esters. The problem is to convert acylmalonic esters (II) into their acids (III), preferably without recourse to aqueous hydrolysis; thermal degradation of the latter then yields the ketones (IV). We described in Part I (*J.*, 1950, 322) the use of acidolysis for the case where R = H and R′ = Et, and in Part II (*J.*, 1950, 325) and in subsequent papers a more general method whereby the benzyl esters (II; R′ = CH_2Ph) are catalytically hydrogenated to the free acids (III) which, on being heated, furnish the ketones (IV). The last method is

$$\underset{\text{(I)}}{R{\cdot}CH(CO_2R')_2} \xrightarrow{R''{\cdot}COCl} \underset{\text{(II)}}{R''{\cdot}CO{\cdot}CR(CO_2R')_2} \longrightarrow \underset{\text{(III)}}{R''{\cdot}CO{\cdot}CR(CO_2H)_2} \longrightarrow \underset{\text{(IV)}}{R''{\cdot}CO{\cdot}CH_2R}$$

satisfactory in many cases, but applies only to the preparation of ketones containing functional groups resistant to hydrogenation, and is also limited by rather difficult and exacting techniques. We therefore attempted to extend the synthesis in a more general manner; when these experiments were almost completed Fonker and W. S. Johnson

* Part V, *J.*, 1951, 2758.

(*J. Amer. Chem. Soc.*, 1952, **74**, 831) reported an elegant new method employing di-*tert.*-butyl malonate.

Malonic esters of tetrahydropyran-2-ol appeared attractive on account of the mild conditions under which it was expected that they would undergo hydrolysis (cf. Jones and Taylor, *Quart. Reviews*, 1950, 207) although, as will be seen, the investigation developed in another direction and we have not examined this last possibility.

Reaction of 2 : 3-dihydropyran and carboxylic acids appears to have been restricted hitherto to the preparation of the *p*-nitrobenzoate (Woods and Kramer, *J. Amer. Chem. Soc.*, 1947, **69**, 2246) and the acetate, the latter formed in 60% yield by refluxing a mixture of dihydropyran and acetic acid for a short time (Bremner and Jones, B.P. 606,764). We have confirmed the yield in the latter preparation by analytical methods and by direct isolation of the product by distillation at low temperatures. On distillation at atmospheric pressure, however, the acetate suffered partial decomposition, giving a mixture of the ester, dihydropyran, and acetic acid in approximately the same proportions as were obtained by interaction of dihydropyran and acetic acid at the boiling point.

We next examined the influence of acid catalysts, since these have been shown to be effective in the preparation of ethers of tetrahydropyran-2-ol (Woods and Kramer, *loc. cit.*) and, indeed, at room temperature in the presence of a trace of *m*-xylenesulphonic acid, the addition proceeded rapidly with evolution of heat to completion. The reaction is therefore catalysed by hydrogen ions and the position of equilibrium is markedly temperature-dependent, being almost completely in favour of ester at room temperature. The ease of preparation and pyrolytic decomposition of these esters under such mild conditions offers a new method for the protection of carboxylic acid groupings and with its aid a new ketone synthesis has been evolved. The malonic acid is suspended in benzene and brought into reaction with an excess of dihydropyran in the presence of a trace of sulphuric acid, a rapid exothermic reaction occurring with dissolution of the acid. After a short time, solvent and excess of dihydropyran are removed under reduced pressure to give (I; R′ = tetrahydro-2-pyranyl). The latter is then converted into its sodio-derivative with metallic sodium and the acid chloride added, all operations being conducted below 40°. Refluxing the resultant mixture, preferably in the presence of a small amount of acetic acid, then brings about irreversible degradation of the keto-ester to ketone, carbon dioxide and, presumably, dihydropyran.

In this manner we prepared the simple ketones 1-phenyltetradecan-3-one (*n*-dodecanoyl chloride and benzylmalonic acid; 60%), 1-phenyldecan-1-one (benzoyl chloride and *n*-octylmalonic acid; 50%), tetracos-1-en-11-one (undec-10-enoyl chloride and *n*-dodecylmalonic acid; 76%), 13-ketotricos-22-enoic acid * (undec-10-enoyl chloride and undecane-1 : 1 : 11-tricarboxylic acid; 75%), and ethyl 2-ketoundecanoate (ethoxalyl chloride and *n*-octylmalonic acid; 65%); the last ester was hydrolysed in good yield to the known parent α-keto-acid.

In extending the method to ketones which are more difficult of access by other reactions we obtained 2-chlorodecan-3-one (α-chloropropionyl chloride and *n*-hexylmalonic acid; 92%), 1-phenyldec-1-yn-3-one (phenylpropiolyl chloride and *n*-hexylmalonic acid; 85%), trideca-2 : 4-dien-6-one (sorboyl chloride and *n*-hexylmalonic acid; 90%), and ethyl *trans*-4-ketoheptadec-2-enoate (ethyl fumaryl chloride and *n*-dodecylmalonic acid; 45%).

Acid anhydrides may also be used, as shown by the use of glutaric anhydride and *n*-amylmalonic acid to give 5-ketoundecanoic acid in 45% yield. Finally, we extended the method to β-keto-esters and prepared, by slightly modified procedures, ethyl 3-ketononoate (*n*-heptanoyl chloride and ethyl hydrogen malonate; 77%) and ethyl 3-keto-2-methyltetradecanoate (*n*-dodecanoyl chloride and ethyl hydrogen methylmalonate; 50%).

It will be noted that the yields described above were somewhat variable and except when anhydrides were used it is probably not fortuitous that they increased as our experience of the method grew. This is not clear on inspection since the experiments are not set out in chronological order, and in no case was any preparation repeated.

In the Experimental section many derivatives, as well as some further reactions of the ketones prepared in this manner, are described.

* Geneva numbering, CO_2H = 1, throughout.

Experimental

Light petroleum refers throughout to the fraction of b. p. 60—80°. Benzene was " AnalaR " material stored over sodium wire.

Dihydropyran was supplied by Imperial Chemical Industries Limited and was purified by distillation through a column, material of b. p. 85—86° being collected.

Reaction of Dihydropyran and Acetic Acid.—(1) *In absence of catalyst.* A mixture of dihydropyran (84 g., 1 mol.) and redistilled glacial acetic acid (30 g., 0·5 mole) was refluxed for 4 hours; determinations of free acidity of the reaction mixture showed that after 1 hour the amount of free acid had dropped to one-third of the initial amount and was unaffected by further refluxing. The products of reaction were worked up as described in B.P. 606,764.

(2) *In presence of* m-*xylenesulphonic acid.* To dihydropyran (84 g., 1 mole) and *m*-xylenesulphonic acid (5 mg.), stirred in absence of moisture, acetic acid (30 g., 0·5 mole) was added dropwise with stirring during 0·5 hour, the temperature of the reaction mixture rising to 40°. After 0·5 hour at room temperature, at least 99% of the acetic acid had reacted, and the product was neutralised by stirring it with a slurry of potassium carbonate (2 g.) in water (4 ml.) and, after decantation, was distilled. The yield of tetrahydropyranyl acetate, b. p. 42—43°/1 mm., n_D^{20} 1·4378, was 62 g. (90%).

General Method for Ketone Synthesis.—The requisite malonic acid (0·05 mole) was added in portions to a solution of dihydropyran (0·075 mole per carboxyl grouping in the malonic acid) in benzene (50 ml.) containing concentrated sulphuric acid (1 drop), with cooling to <30°. Heat was evolved during the addition and for some time afterwards. In all cases, the reaction was substantially complete when a clear solution was obtained, but in practice the mixture was left at room temperature for a further 0·5 hour. At this stage we frequently determined free acidity to confirm the almost complete conversion into ester. Traces of free acid were then removed by shaking or stirring the solution with solid potassium hydroxide (4 g.) for 0·5 hour and the solution was decanted from inorganic material. Solvent and excess of dihydropyran were removed by distillation *in vacuo* (bath-temp. <30°) and the residual ester in benzene was (50 ml.) added to sodium powder (0·05 g.-atom) in benzene (100 ml.), with cooling to <35°. When dissolution of the metal was complete, a solution of the acid chloride (0·05 mole) in benzene (50 ml.) was added and, after 0·5 hour at room temperature, acetic acid (5 ml.) was added and the solution boiled under reflux until evolution of carbon dioxide ceased (*ca.* 1·5 hours). The cooled mixture was washed with water or, if the final product was neutral, with dilute alkali. After removal of solvent, the resulting material was purified by distillation or crystallisation.

The addition of acetic acid is optional but, since it reduces the time necessary for decarboxylation and rarely attacks the ketonic compound, is advantageous.

The following were obtained from the materials and in the yields stated on p. 3946 :

1-*Phenyltetradecan*-3-*one*, an oil, b. p. 170—172°/0·8 mm., which solidified and then crystallised from methanol in thin plates, m. p. 31° (Found : C, 83·9; H, 11·0. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%).

1-*Phenyldecan*-1-*one*, an oil, b. p. 142—146°/2 mm., which solidified and then separated from methanol in slender needles, m. p. 33—33·5° (Found : C, 82·7; H, 10·0. $C_{16}H_{24}O$ requires C, 82·7; H, 10·3%). Its *phenylsemicarbazone* crystallised from methanol–ethyl acetate in small needles, m. p. 110° (Found : N, 11·5. $C_{23}H_{31}ON_3$ requires N, 11·5%).

Tetracos-1-*en*-11-*one* was obtained as a solid mass (m. p. 57°) which separated from ethyl acetate in plates, m. p. 57° (Found : C, 82·1; H, 13·0. $C_{24}H_{46}O$ requires C, 82·2; H, 13·2%). Catalytic hydrogenation with palladium oxide in ethyl methyl ketone furnished *tetracosan*-11-*one* as lustrous plates (from methanol), m. p. 64—64·5° (Found : C, 81·6; H, 13·4. $C_{43}H_{48}O$ requires C, 81·7; H, 13·7%) which formed an *oxime*, prisms (from methanol), m. p. 38° (Found : N, 3·7. $C_{24}H_{49}ON$ requires N, 3·8%). On Wolff–Kishner reduction using Huang-Minlon's modified conditions (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) the unsaturated ketone furnished *tetracos*-1-*ene* (90%) as leaflets, m. p. 46—46·5°, from ethyl acetate (Found : C, 85·7; H, 14·1. $C_{24}H_{48}$ requires C, 85·7; H, 14·3%).

2-*Chlorodecan*-3-*one* was prepared by the general procedure except that reaction with the acid chloride, which was added in one portion, was carried out at 0°, after which the mixture was allowed to rise to room temperature overnight. The product was a colourless oil (92%), b. p. 70—71°/1 mm., n_D^{20} 1·4512 (Found : C, 63·2; H, 10·0. $C_{10}H_{19}OCl$ requires C, 63·0; H, 10·0%).

1-*Phenyldec*-1-*yn*-3-*one*, a pale yellow oil, b. p. 127—128°/0·5 mm., n_D^{20} 1·5275 (Found : C, 83·4; H, 9·1. $C_{16}H_{20}O$ requires C, 84·2; H, 8·8%). On hydrogenation in ethyl methyl ketone

over palladium oxide, the product absorbed 2 mols. of hydrogen and gave 1-*phenyldecan*-3-*one*, b. p. 128—129°/0·5 mm., n_D^{20} 1·4920 (Found: C, 82·6; H, 10·4. $C_{16}H_{24}O$ requires C, 82·7; H, 10·4%), which formed a 2 : 4-*dinitrophenylhydrazone*, orange plates (from ethanol), m. p. 73° (Found: C, 64·1; H, 6·9; N, 14·1. $C_{22}H_{28}O_4N_4$ requires C, 64·1; H, 6·8; N, 13·6%).

Trideca-2 : 4-dien-6-one, a pale yellow oil, b. p. 105—106°/1 mm., n_D^{20} 1·4860 ($\lambda_{max.}$ 273 mμ, $\varepsilon_{max.}$ 19,300 in ethanol). In spite of repeated efforts we were unable to obtain reproducible or the required analytical figures (Found: C, 76·0—78·5; H, 10·9—11·6%. Calc. for $C_{13}H_{22}O$: C, 80·4; H, 11·4%), although by oxime titration the material was at least 98% pure. It formed a 4-*phenylsemicarbazone*, pale yellow needles (from methanol), m. p. 123—124° (Found: C, 73·5; H, 9·1; N, 13·3. $C_{20}H_{29}ON_3$ requires C, 73·4; H, 8·9; N, 12·9%).

Ethyl 2-*ketoundecanoate*, a colourless oil, b. p. 110—111°/1·3 mm., n_D^{20} 1·4374 (Found: C, 68·2; H, 10·3. $C_{13}H_{24}O_3$ requires C, 68·4; H, 10·5%), formed an *oxime*, needles (from light petroleum), m. p. 66—67° (Found: N, 5·85. $C_{13}H_{25}O_3N$ requires N, 5·8%). The ester (4 g.) was refluxed with constant-boiling hydrochloric acid (50 ml.) and acetic acid (20 ml.) for 6 hours. When the cooled solution was poured into water the product crystallised (3 g.). 2-Ketoundecanoic acid crystallised from light petroleum in glistening plates, m. p. 54·0—54·5° (Found: C, 66·2; H, 9·8. Calc. for $C_{11}H_{20}O_3$: C, 66·0; H, 10·0%), and formed a *phenylhydrazone*, almost colourless nacreous plates (from light petroleum), m. p. 93·5—94·0° (Found: N, 9·7. $C_{17}H_{26}O_2N_2$ requires N, 9·7%); on reduction in ethyl methyl ketone over palladium oxide, it gave 2-hydroxyundecanoic acid, needles (from light petroleum), m. p. 68·5—69° (lit., 69°).

13-*Ketotricos*-22-*enoic acid* was obtained a solid (m. p. 75—80°) after washing of the final reaction product with 70% ethanol. The pure acid was obtained by crystallisation from light petroleum, from which it separated in rectangular plates, m. p. 85—86° (Found: C, 75·4; H, 11·3. Calc. for $C_{23}H_{42}O_3$: C, 75·4; H. 11·5%). It formed a p-*bromophenacyl* ester, colourless plates (from ethyl acetate), m. p. 85° (Found: C, 66·0; H, 8·4. $C_{31}H_{47}O_4Br$ requires C, 66·1; H, 8·3%). On catalytic reduction, as previously, it gave 13-*ketotricosanoic acid*, plates (from methanol), m. p. 93—93·5° (Found: C, 74·9; H, 11·7. $C_{23}H_{44}O_3$ requires C, 74·9; H, 11·9%), and on Wolff–Kishner reduction (Huang-Minlon, *loc. cit.*) it furnished tricos-22-enoic acid, rectangular plates (from light petroleum), m. p. 73·5—74·0° (Found: C, 78·7; H, 12·6. Calc. for $C_{23}H_{44}O_2$: C, 78·4; H, 12·5%). E. Stenhagen (*Arkiv Kemi*, 1949, **13**, 99) reports m. p.s of 86·5—86·7° and 74·3—74·5° for the keto-enoic and the enoic acid respectively. A sample of the latter was catalytically reduced in the usual manner to *n*-tricosanoic acid, m. p. 79°, undepressed on admixture with an authentic specimen (Ames, Bowman, and Mason, *J.*, 1950, 174).

Ethyl trans-4-*ketoheptadec*-2-*enoate* [from ethyl fumaryl chloride (Eisner, Elvidge, and Linstead, *J.*, 1951, 1508) and *n*-dodecylmalonic acid] distilled as a colourless liquid, b. p. 170—180°/1 mm., which rapidly solidified and then crystallised from methanol in clusters of needles, m. p. 38—38·5°, $\lambda_{max.}$ 222 mμ, $\varepsilon_{max.}$ 11,900 in ethanol (Found: C, 73·4; H, 10·7. $C_{19}H_{34}O_3$ requires C, 73·5; H, 11·0%). Attempts to obtain the free acid by alkaline or acid hydrolysis led to coloured gums.

5-*Ketoundecanoic Acid*.—*n*-Amylmalonic acid (0·05 mole) was converted into the sodio-bistetrahydropyranyl ester in benzene according to the general method, and glutaric anhydride (5·7 g., 0·05 mole) in benzene (20 ml.) added. After 1 hour at room temperature the reaction mass solidified to a colourless gel. Acetic acid (20 ml.) was then added and the mixture boiled under reflux until evolution of carbon dioxide ceased (0·5 hour). Water was added and the organic extract evaporated to dryness under reduced pressure, to give an oil which solidified (10 g.). Crystallisation from ethyl acetate and then ethyl acetate–light petroleum furnished the keto-acid (4 g., 45%) as colourless plates, m. p. 59—60° (Found: C, 66·2; H, 10·0. Calc. for $C_{11}H_{20}O_3$: C, 66·0; H, 10·1%). It formed p-*bromophenacyl* ester, laminæ (from moist ethanol), m. p. 78—79° (Found: C, 57·5; H, 6·2. $C_{19}H_{25}O_4Br$ requires C, 57·4; H, 6·3%).

Ethyl 3-*Ketononoate*.—Ethyl hydrogen malonate (b. p. 101—102°/2 mm., n_D^{20} 1·4295; 26 g., 0·2 mole) was added slowly to a solution of dihydropyran (25 g.) in benzene (30 ml.) containing 3 drops of a 10% solution of *m*-xylenesulphonic acid in methanol, during 0·5 hour; the initial and the final temperature of the mixture were 16° and 34° respectively. Excess of solvent and dihydropyran were removed *in vacuo* and the colourless residual ester converted into its sodio-derivative and treated with *n*-heptanoyl chloride (0·2 mole), as previously. After decarboxylation and isolation in the usual manner, the product was distilled, the fraction of b. p. 88—90°/1·5 mm. (14 g., 77%) being collected. This material, which was the almost pure keto-ester, was purified with very little loss by washing its solution in light petroleum with sodium hydrogen

carbonate solution; it then distilled at 96—97°/3 mm. and had n_D^{20} 1·4415 (Found: C, 66·4; H, 10·1. Calc. for $C_{11}H_{20}O_3$: C, 66·0; H, 10·1%). It formed a phenylpyrazolone, m. p. 83°; Wahl and Doll (*Bull. Soc. chim.*, 1913, **13**, 275) reported m. p. 83—84°.

Ethyl 3-Keto-2-methyltetradecanoate.—This *ester* was prepared from *n*-dodecanoyl chloride and ethyl hydrogen methylmalonate (cf. Breslow, Baumgarten, and Hauser, *J. Amer. Chem. Soc.*, 1944, **66**, 1287) in the usual manner, the crude product in light petroleum being washed with aqueous sodium hydrogen carbonate before distillation; it was obtained as a colourless oil, b. p. 144—145°/1·5 mm., n_D^{20} 1·4450 (Found: C, 72·6; H, 11·1. $C_{17}H_{32}O_3$ requires C, 71·8; H, 11·3%). It furnished a p-*nitrophenylpyrazolone*, yellow prisms (from light petroleum–ethyl acetate), m. p. 85—86° (Found: C, 67·6; H, 8·5. $C_{21}H_{31}O_3N_3$ requires C, 67·5; H, 8·4%). The keto-ester (2·5 g.) was hydrolysed by refluxing it with acetic acid (15 ml.) and sulphuric acid (5 ml. of 80%) for 1 hour. The cooled mixture was poured into water and the material isolated in the usual manner as a solid (1·5 g.; m. p. 32°) which crystallised from methanol in glistening plates, m. p. 33—33·5°. Blaise and Guerick (*Bull. Soc. chim.*, 1903, **29**, 1208) give the m. p. of tetradecan-3-one as 34°.

We are indebted to the directors of Messrs. A. Boake, Roberts & Co. Ltd. for facilities provided to one of us (W. D. F.) for carrying out much of the work described herein.

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759. *Griseofulvin. Part I.*

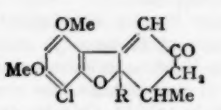
By John Frederick Grove, J. MacMillan, T. P. C. Mulholland, and M. A. Thorold Rogers.

The structures proposed for griseofulvin, $C_{17}H_{17}O_6Cl$, by Oxford, Raistrick, and Simonart (*Biochem. J.*, 1939, **33**, 240) and by Grove and McGowan (*Nature*, 1947, **160**, 574) are inconsistent with the ultra-violet and infra-red absorption spectra. Grove and McGowan's suggestion (*Chem. and Ind.*, 1949, 647), based on spectroscopic data, that griseofulvin is the methyl ether of a 1 : 3-diketone has been proved conclusively by catalytic reduction of griseofulvic acid, $C_{16}H_{15}O_6Cl$, to two neutral non-lactonic alcohols, $C_{16}H_{19}O_6Cl$ and $C_{16}H_{19}O_5Cl$, and by other evidence. The formation of decarboxygriseofulvic acid by the action of alkali on griseofulvic acid is shown by ultra-violet and infra-red spectroscopic evidence to involve a rearrangement of the molecule.

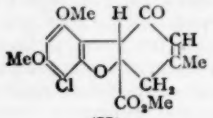
Griseofulvin, $C_{17}H_{17}O_6Cl$, m. p. 220°, $[\alpha]_{5790}^{19}$ +354°, a colourless neutral compound containing three methoxyl groups, was isolated from the mycelium of *Penicillium griseofulvum* Dierckx by Oxford, Raistrick, and Simonart (*Biochem. J.*, 1939, **33**, 240). Subsequently, it was isolated from *P. janczewskii* Zal. [= *P. nigricans* (Bainier) Thom] and its unique biological activity on moulds noted by Brian, Curtis, and Hemming (*Trans. Brit. Mycol. Soc.*, 1946, **29**, 173; see also Brian, *Ann. Bot.*, 1949, **13**, 59) and McGowan (*Trans. Brit. Mycol. Soc.*, 1946, **29**, 188) who originally called it "curling factor" before the identity with griseofulvin was established (Grove and McGowan, *Nature*, 1947, **160**, 574; Brian, Curtis, and Hemming, *Trans. Brit. Mycol. Soc.*, 1949, **32**, 30).

Although the chemical and biological properties of "curling factor" and griseofulvin were identical, the analytical data and molecular-weight determinations quoted by McGowan (*loc. cit.*) in support of his original formula $C_{20}H_{20}O_9$ agreed more closely with $C_{20}H_{19}O_7Cl$ than with $C_{17}H_{17}O_6Cl$. However, a careful reinvestigation has established the empirical formula as $C_{17}H_{17}O_6Cl$, in agreement with the earlier work of Oxford *et al.* and this is supported by molecular-weight determinations by both the Rast and crystallographic methods (the latter by Dr. A. F. Wells). Nevertheless, the structure (I) tentatively proposed by Oxford *et al.* (*loc. cit.*) is not entirely satisfactory even on the basis of the facts which they reported, and we have accumulated considerable evidence which cannot be reconciled with it. We have repeated practically all the experimental work

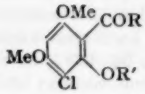
described by Oxford *et al.* and agree with the great majority of it. These facts alone, however, are not sufficient to support a structural formula.



(I; R = CO_2Me)
(Ia; R = H)



(II)



(III)

Oxford *et al.* showed that griseofulvin contained an ethylenic bond and a chemically reactive carbonyl group and these observations have been confirmed by microhydrogenation and preparation of a crystalline 2 : 4-dinitrophenylhydrazone. In addition, griseofulvin

FIG. 1.

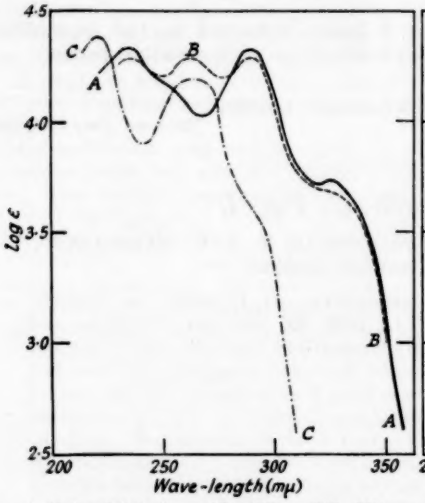


FIG. 2.

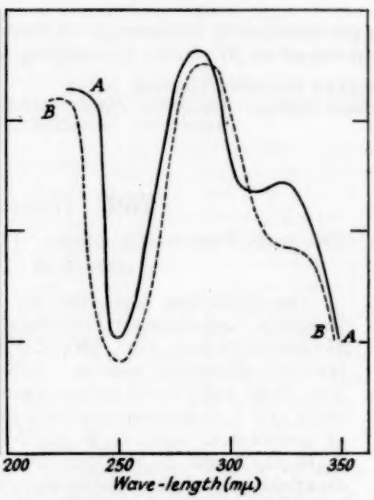


FIG. 1. *A, Griseofulvin* ($\lambda_{max.}$ 324, 291, ~252, 236 mμ; log ε 3·72, 4·34, 4·10, 4·33 *respectively*). *B,* iso-*Griseofulvin* ($\lambda_{max.}$ 326, 291, 263, 235 mμ; log ε 3·71, 4·29, 4·29, 4·28 *respectively*). *C, Decarboxy-griseofulvic acid* ($\lambda_{max.}$ ~295, 265, 220 mμ; log ε 3·47, 4·20, 4·39 *respectively*) (*all in methanol*).

FIG. 2. *A, Griseofulvic acid reduction product A in methanol. B, Methylphloracetophenone.*

reacts normally with Girard's reagent P, forming a derivative from which it can be recovered unchanged. With semicarbazide in pyridine griseofulvin gave, not the normal semicarbazone, but an isomeric base which was readily hydrolysed by dilute mineral acids to griseofulvic acid. The properties of this derivative suggest that it is a pyrazoline although it did not respond to the Knorr test. Oxford *et al.* reported evidence suggesting that the double bond in griseofulvin was conjugated with the carbonyl group, and the reaction with semicarbazide provides additional evidence for the presence of an αβ-unsaturated ketone grouping. Griseofulvin reacts readily with bromine in chloroform, but hydrogen bromide is eliminated and the product is bromogriseofulvin.

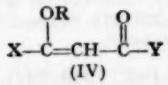
Grove and McGowan (*loc. cit.*) pointed out that structure (II), a slight modification of (I), accounted more satisfactorily for the properties of griseofulvin as then known. But consideration of the ultra-violet and infra-red absorption spectra of griseofulvin and some of its derivatives led these authors (*Chem. and Ind.*, 1949, 647) ultimately to reject both structures. The ultra-violet absorption spectrum of griseofulvin (Fig. 1) showed that the αβ-unsaturated ketone system postulated by Oxford *et al.* could not be conjugated with the aromatic nucleus in griseofulvin as in (I). Neither did the absorption of griseofulvin agree particularly well with that predicted for (II). Rather, it was typical of a compound in

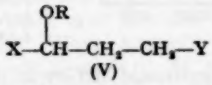
which phloroglucinol and carbonyl chromophores were conjugated, as in pinobanksin dimethyl ether (Lindstedt, *Acta Chem. Scand.*, 1950, **4**, 772) and some of the derivatives and analogues of rottlerin investigated by Morton and Sawires (*J.*, 1940, 1052), and it strongly suggested that griseofulvin contained the partial structure (III). The curve for methylphloracetophenone taken from the paper of Morton and Sawires is plotted in Fig. 2.

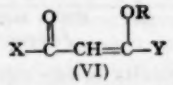
There is, moreover, chemical evidence for the inadequacy of formulæ (I) and (II). Thus, while griseofulvin on mild hydrolysis with aqueous alcoholic alkali gives griseofulvic acid, $C_{16}H_{15}O_6Cl$, one of the reduction products, tetrahydrodeoxygriseofulvin, is very resistant to hydrolysis and this stability cannot easily be dismissed in terms of steric hindrance (cf. Oxford *et al.*, *loc. cit.*; see also Part VI, *J.*, 1952, 3994). Further, the fact that on slightly more vigorous hydrolysis with aqueous alkali griseofulvic acid gives as one of the products decarboxygriseofulvic acid, $C_{15}H_{15}O_4Cl$, cannot be taken as proving the presence of the carboxylic acid group. In fact, the stability which we find griseofulvic acid possesses towards acid hydrolysis (24 hours' heating under reflux in 6N-sulphuric acid and 70% recovery of griseofulvic acid), suggests that the carbon dioxide lost in the alkaline hydrolysis is derived from a carboxyl group which makes its appearance as a result of a molecular rearrangement under alkaline conditions. Support for this is obtained from a comparison of the ultra-violet absorption curves of griseofulvin and decarboxygriseofulvic acid (Fig. 1) which show a profound alteration in the chromophoric system to have occurred (Grove and McGowan, *Chem. and Ind.*, *loc. cit.*), as well as from the infra-red spectra (see below) of these two compounds (Fig. 3).

In addition, the ultra-violet absorption of decarboxygriseofulvic acid is clearly inconsistent with the structure (I*a*) suggested for this compound by Oxford *et al.* A compound in which the αβ-unsaturated ketone grouping is conjugated with the aromatic nucleus should show a strong absorption band in the region of 330 mμ (Grove and McGowan, *loc. cit.*).

The difference in behaviour of griseofulvin and tetrahydrodeoxygriseofulvin towards hydrolysis caused Grove and McGowan to suggest that griseofulvin contained the grouping (IV; R = Me), being a methyl enol ether of a 1 : 3-diketone, griseofulvic acid (IV; R = H). Tetrahydrodeoxygriseofulvin (V; R = Me) in which the methoxyl group is attached to a saturated carbon atom would then resist hydrolysis. Oxford *et al.* observed that an isomer, m. p. 200—201°, $[\alpha]_{5790}^{19}$ +223°, of griseofulvin was formed, mixed with an approximately equal amount of griseofulvin, when griseofulvic acid or norgriseofulvic acid was methylated with diazomethane. It appeared likely on the above hypothesis that *iso*griseofulvin would prove to be the isomeric methyl ether (VI), although no evidence was offered at that time. We have now shown that *iso*griseofulvin can be made easily and in good yield by the action of methanolic hydrochloric acid on griseofulvin. *iso*Griseofulvin is easily hydrolysed by dilute aqueous-alcoholic alkali to griseofulvic acid, which has the same optical rotation and configuration as that prepared from griseofulvin; the isomerism is thus not connected with asymmetry round a particular carbon atom, but arises from the presence of a tautomeric system in griseofulvic acid. As is then to be expected, the ultra-violet absorption of *iso*griseofulvin (Fig. 1) is similar to that of griseofulvin: nevertheless, *iso*griseofulvin shows an additional and characteristic band at 263 mμ. *iso*Griseofulvin also differs from griseofulvin in that it does not readily form derivatives with ketonic reagents.


(IV)


(V)


(VI)

Recent work on the correlation of absorption frequency and structure for the C=O and –OH stretching vibrations has been summarised by Grove and Willis (*J.*, 1951, 877). Normal carboxylic esters generally absorb between 1715 (conjugated) and 1745 $cm.^{-1}$ (unconjugated). These frequencies may be raised by the presence of powerful electron-attracting substituents (*e.g.*, NO_2) or lowered by intramolecular hydrogen bonding (chelation); however, neither of these complications is present in the griseofulvin molecule. Griseofulvin (Fig. 3*b*) has no absorption bands in the carboxylic ester range, and the

highest >C=O absorption occurs at 1700 cm.$^{-1}$. Carboxylic acids in the solid (dimeric) state show a broad absorption in the region 2500—2700 cm.$^{-1}$ attributed to –OH stretching vibrations and a band in the range 1680 (conjugated) to 1720 cm.$^{-1}$ (unconjugated) due to the >C=O group. The highest absorption frequency in the double-bond stretching region of griseofulvic acid (Fig. 3*a*) occurs at 1655 cm.$^{-1}$; the compound does not absorb in the region 2500—2700 cm.$^{-1}$ but has a strong alcoholic (or enolic) –OH absorption at 3225 cm.$^{-1}$.

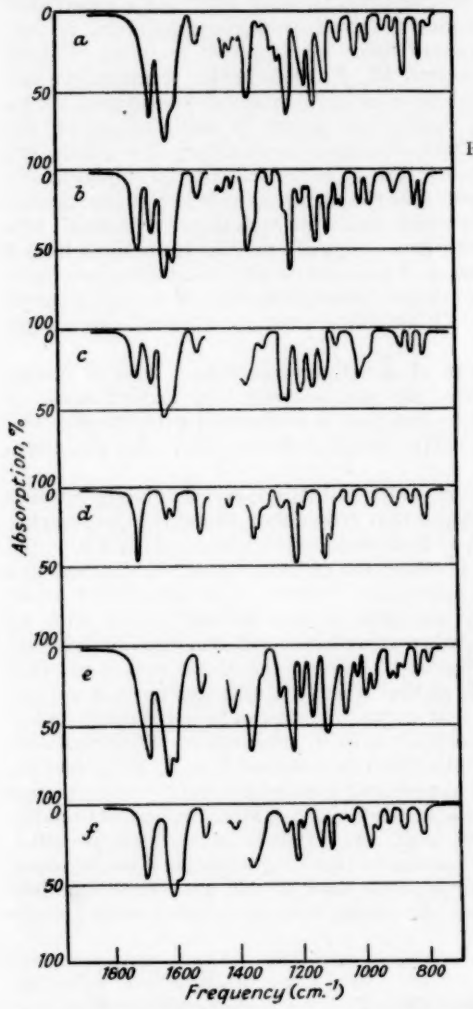
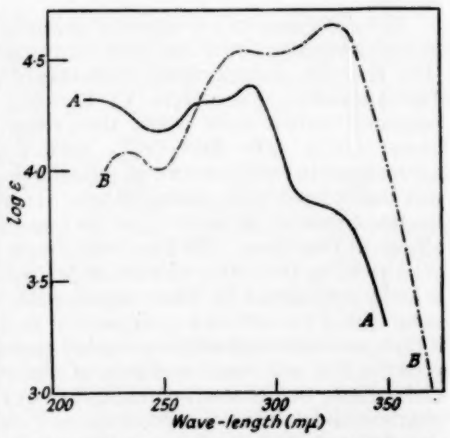


FIG. 3. *a, Griseofulvic acid; b, griseofulvin; c, isogriseofulvin; d, decarboxygriseofulvic acid; e, griseofulvic acid reduction product A; f, griseofulvic acid reduction product C.*

FIG. 4.



Norgriseofulvic acid, (A) in methanol ($\lambda_{max.}$ 332, 290, 269, 223 mμ; log ε 3·77, 4·38, 4·32, 4·32 *respectively*) *and (B) in* 0·1N-*sodium hydroxide* ($\lambda_{max.}$ 327, 277, 234 mμ; log ε 4·65, 4·53, 4·08 *respectively*).

These results, briefly reported by Grove and McGowan (*Chem. and Ind.*, 1949, 647), indicate the absence of carboxylic ester and carboxylic acid groups in griseofulvin and griseofulvic acid respectively, and can be interpreted as supporting the hypothesis outlined above. Furthermore, the presence of two carbonyl groups absorbing at 1700 and 1650 cm.$^{-1}$, respectively, in griseofulvin is clearly shown, and one of these persists in the spectra of those compounds in which the reactive carbonyl group has been removed, for example, by hydrogenation (see below; see also Part V, *J.*, 1952, 3987).

The infra-red spectra of griseofulvin and *iso*griseofulvin (Figs. 3*b* and *c*) are very similar,

particularly in the double-bond stretching region, *iso*griseofulvin showing two carbonyl bands at 1704 and 1658 cm.$^{-1}$ respectively. Griseofulvin, *iso*griseofulvin, and griseofulvic acid all show an intense broad band between 1580 and 1620 cm.$^{-1}$, arising presumably from unsaturation in the skeletal ring system. These intense bands are absent in the spectrum of decarboxygriseofulvic acid (Fig. 3*d*), which shows >C=O absorption at 1710 cm.$^{-1}$ attributed to an unconjugated six-membered ring keto-group and no OH absorption.

Set against the spectroscopic evidence may be mentioned three facts which, though inconclusive, might suggest the presence of a carboxylic acid group in griseofulvic acid. Pyrolysis of griseofulvic acid gives some carbon dioxide, but the amorphous residue is not decarboxygriseofulvic acid and it may be argued that a profound structural alteration is involved. Griseofulvic acid may be "esterified" with methanolic hydrochloric acid under Fischer–Speier conditions; methylation under these conditions is, however, merely an indication of acidity (griseofulvic acid has K 3·2 × 10^{-5} at 18°) and, though not a normal method of preparing enol ethers, has analogies (cf. the *O*-alkylation of phloroglucinol). Thirdly, a keto–enol system of the type postulated might be expected to give more than a pale orange colour with ferric chloride; however, Morgan and Drew (*J.*, 1924, **125**, 752) reported, and it has been confirmed, that dimedone, in common with some other cyclic

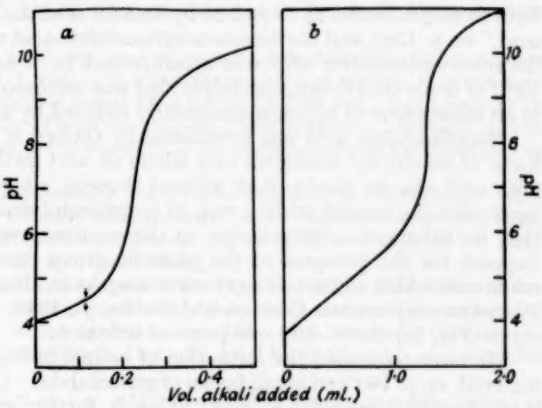
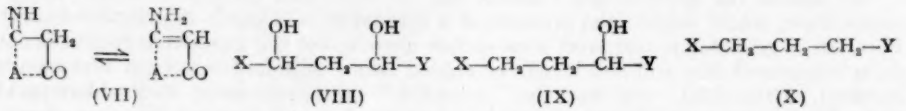


FIG. 5. *a, Griseofulvic acid, c* = 1·1 × 10^{-3}M *in water; b, norgriseofulvic acid, c* = 2·25 × 10^{-3}M *in aqueous alcohol.*

1 : 3-diketones, gives no colour with ferric chloride in an alcoholic solution of concentration comparable to that attainable with griseofulvic acid.

However, further observations provide conclusive evidence against the presence of a carboxylic acid residue. First, griseofulvin and griseofulvic acid give negative reactions in the hydroxamic acid test for carboxylic ester and acid groupings. Secondly, griseofulvic acid is a mild reducing agent and is oxidised by warm ammoniacal silver and yellow mercuric oxide; griseofulvin has no reducing activity. Thirdly, griseofulvin reacts with ammonia in methanol to give a compound, griseofulvamine, $C_{16}H_{16}O_5NCl,H_2O$ which is certainly not an amide. The properties of this substance, which contains only two methoxyl groups, are typical of compounds formed by cyclic β-diketones, *e.g.*, dimedone (Haas, *J.*, 1906, **89**, 187) with ammonia and are in accord with the structures of the type (VII). Finally, reduction of griseofulvic acid provides the strongest evidence against the presence of a carboxylic acid group. When Adams's platinum oxide catalyst in acetic acid was used, two neutral non-lactonic alcohols, $C_{16}H_{19}O_6Cl$ (A) and $C_{16}H_{19}O_5Cl$ (B), were isolated together with small amounts of a neutral non-lactonic compound, $C_{16}H_{19}O_4Cl$ (C). If the acidic component in griseofulvic acid is (IV; R = H), these compounds can be written with the partial structures (VIII) (IX or V; R = H), and (X), respectively. The reduction product B was oxidised by chromic acid to the corresponding ketone, $C_{16}H_{17}O_5Cl$, indicating that the hydroxyl group is secondary. The ultra-violet absorption curve of the reduction product A (Fig. 2) shows that the main chromophoric system (III) of griseofulvin is unaffected by the reduction and since the chemically unreactive carbonyl

group of griseofulvin can be identified in A by its infra-red spectrum (Fig. 3*e*; band at 1685 cm.$^{-1}$) it follows that this carbonyl group must be the one in the partial structure (III). This unreactive carbonyl group can also be identified in the spectra of the reduction products B (band at 1682 cm.$^{-1}$) and C (Fig. 3*f*; band at 1695 cm.$^{-1}$); A and B show typical alcoholic –OH absorption (at 3401 and 3425 cm.$^{-1}$ respectively), which is absent in the spectrum of reduction product C.



(VII) (VIII) (IX) (X)

It is considered that all the facts reported above are satisfactorily explained by the hypothesis that griseofulvin contains two carbonyl groups, one of which is unreactive chemically. The reactive carbonyl group is contained in the partial structure (IV; R = Me), griseofulvic acid being the corresponding 1 : 3-diketone (IV; R = H, in the enolic form). The formation of decarboxygriseofulvic acid involves a profound rearrangement.

The behaviour of griseofulvin with alkali is complex. In some experiments, the hydrolysis proceeded as described by Oxford *et al.* and the neutral " decarboxygriseofulvic acid," m. p. 138°, and the dibasic norgriseofulvic acid were isolated. In other experiments, decarboxygriseofulvic acid was accompanied by a neutral isomer, m. p. 204—206°; the yield of crude decarboxygriseofulvic acid was increased when the hydrolysis was conducted in an atmosphere of nitrogen and greatly reduced by a stream of air.

Norgriseofulvic acid was formulated by Oxford *et al.* (*loc. cit.*) as a phenolic acid. We know of no strictly analogous case where an aryl methyl ether group has been hydrolysed with such ease by dilute alkali without showing a high lability to acid. Nevertheless, we agree that the second acidic group in norgriseofulvic acid is indeed phenolic, and consider that its enhanced acidity is due to the environment of the remainder of the molecule. Support for the presence of the phenolic group comes from the ultra-violet absorption maximum which shifts to longer wave-lengths in alkaline solution (Fig. 4), as occurs with hydroxyacetophenones (Morton and Stubbs, *J.*, 1940, 1347). The potentiometric titration curve (Fig. 5*b*) shows only one point of inflexion.

We have confirmed the formation of orcinol in high yield (together with a little acidic material, m. p. 180°) on alkali fusion of griseofulvin. On the other hand, none was obtained from decarboxygriseofulvic acid. This is further evidence that rearrangement of the molecule is involved in the formation of the latter.

Experimental

M. p.s are corrected. Mixed m. p. determinations with griseofulvic acid are unreliable and identification was established, except where stated, by comparison of the *X*-ray powder patterns.

Infra-red spectra of solids were obtained in Nujol " mulls " in the apparatus described by Grove and Willis (*loc. cit.*). Calibration accuracy : ±3 at 1700 cm.$^{-1}$, ±10 at 3000 cm.$^{-1}$. Concentration and thickness of " mulls " were not determined and it is not possible to compare intensities in the spectrum of one compound with another.

Microanalyses are by Drs. Strauss and Weiler, Oxford, by Mr. W. Brown, Imperial Chemical Industries Limited, Butterwick Research Laboratories, and by the Analytical Department, Imperial Chemical Industries Limited, Dyestuffs Division.

Crude Griseofulvin.—Initially, crude griseofulvin was supplied by Mr. P. J. Curtis and was obtained by chloroform extraction of the culture filtrates of *P. janczewskii* and *P. griseofulvum*. It contained a new mould metabolite having properties very similar to those of griseofulvin and was identified as the dechloro-analogue, dechlorogriseofulvin (MacMillan, *Chem. and Ind.*, 1951, 719).

Griseofulvin and dechlorogriseofulvin could be separated by chromatography on activated alumina or by fractional crystallisation but both methods were time-consuming and tedious. Accordingly, the large-scale production of griseofulvin from the mycelium of *P. griseofulvum* was undertaken by Dr. C. T. Calam, Imperial Chemical Industries Limited, Dyestuffs Division, to whom we are indebted. Crude griseofulvin from this source did not contain dechloro-

griseofulvin but contained another impurity, identified as mycelianamide (Oxford and Raistrick, *Biochem. J.*, 1948, **42**, 323) by direct comparison with an authentic sample kindly provided by Prof. H. Raistrick.

Griseofulvin.—Griseofulvin, obtained from the mycelium of *P. griseofulvum* Dierckx by the method of Oxford *et al.* (*loc. cit.*), and crystallised from ethanol, was purified further by chromatography on activated alumina. In a typical experiment, griseofulvin (43·5 g.) in benzene (4 l.) was filtered from *ca.* 1·5 g. of insoluble material and chromatographed on a column (21·5 × 2·5 cm.) of alumina of pH 4, activated at 130—140°. A dark impurity was strongly adsorbed at the top of the column. Griseofulvin was only weakly adsorbed and soon started to pass through with the eluant (A). The chromatogram was developed with benzene (300 ml.) containing 1% of ethanol and elution continued until a thin brown band reached the bottom of the column (eluant B). Recovery of the combined eluants A and B gave pure griseofulvin (34·8 g.), m. p. 218—219°, together with a less pure fraction (3·8 g.), m. p. 217—218°. Analytical specimens, further purified by crystallisation from ethanol or benzene, formed needles or prisms, m. p. 220—221°, $[\alpha]_D^{21}$ +337° (*c*, 1·00 in acetone) [Found : C, 58·0, 58·0; H, 5·1, 5·0; Cl, 9·9, 10·1; OMe, 25·8; *C*-Me (Kühn–Roth), 4·1%; *M* (Rast), 355. Calc. for $C_{17}H_{17}O_6Cl$: C, 57·9; H, 4·85; Cl, 10·1; 3OMe, 26·4; *C*-Me, 4·1%; *M*, 352·5].

The unit cell was tetragonal and had *a* 8·93, *c* 19·83 Å. The density, determined by flotation in sodium iodide solution, was 1·462. Hence the molecular weight per unit cell is 1394; *i.e.*, there are four molecules (Found : *M*, 348·5). We are indebted to Dr. A. F. Wells for this information.

On hydrogenation of griseofulvin (4·528 mg.) in the apparatus described by Clauson-Kaas and Limborg (*Acta Chem. Scand.*, 1947, **1**, 884) with a palladium–charcoal catalyst in acetic acid solution, hydrogen equivalent to 1·33 double bonds (0·42 ml. at 23°/749 mm.) was taken up in 10 minutes; this was followed by uptake of a further 0·17 ml. in 50 minutes. This slow uptake has been shown by experiments with model compounds to be characteristic of the reduction of a keto-group (cf. Part V, *loc. cit.*).

Derivatives. Griseofulvin (0·4 g.) and bromine (0·6 g.) were dissolved in chloroform. After 30 minutes the solvent and excess of bromine were removed. The residual *bromo*-derivative, crystallised from ethanol, had m. p. 255° (decomp.) [Found : C, 46·2; H, 3·5; Hal. (1Cl + 1Br), 27·5. $C_{17}H_{16}O_6ClBr$ requires C, 47·2; H, 3·7; Hal., 26·8%].

Griseofulvin in ethanol was treated with an excess of Brady's reagent (*J.*, 1951, 756). After 24 hours, the solution was warmed to 70° and cautiously diluted with water. On cooling, the *monodinitrophenylhydrazone* separated in red needles, m. p. 155—160° (decomp.) (Found : C, 51·6; H, 4·1; N, 10·7. $C_{23}H_{21}O_9N_4Cl$ requires C, 51·8; H, 4·0; N, 10·5%). It was insoluble in warm dilute hydrochloric acid.

Prepared by the method of Oxford *et al.* (*loc. cit.*) and air-dried, the mono-oxime melted at 120° with gas evolution, reset on further heating, and remelted sharply at 224°. A specimen, dried *in vacuo* at 100° for analysis, melted at 225° without previous melting or sintering (Found : C, 55·2; H, 5·0; N, 4·0; Cl, 9·1. Calc. for $C_{17}H_{18}O_6NCl$: C, 55·5; H, 4·9; N, 3·8; Cl, 9·5%).

Reaction with thiosemicarbazide. (*a*) Griseofulvin was recovered unchanged after being heated under reflux for 3 hours with thiosemicarbazide in ethanol.

(*b*) Griseofulvin (0·2 g.) was heated under reflux for 1 hour with Girard reagent P (0·7 g.) in acetic acid (2N in ethanol; 10 ml.), the solution was poured into ice and 2N-sodium hydroxide (10 ml.), and the whole rapidly adjusted to pH 6 (acidification of a portion, at this stage, with 6N-hydrochloric acid precipitated griseofulvin). To the filtered solution (85 ml.) were added thiosemicarbazide (0·8 g.) in 2N-hydrochloric acid (turbidity) and then a further 6 ml. of 2N-acid. The flocculent precipitate, collected after 15 minutes, had m. p. 196—198° (decomp.) with softening at 182°. Extraction with hot benzene (much semi-solid insoluble material) and cooling gave long colourless needles (70 mg.) of a *substance* which, recrystallised twice from benzene, had m. p. 190—200° (decomp.) after softening above 165° (Found : C, 55·45; H, 5·15; N, 8·4. $C_{18}H_{22}O_6N_3SCl,C_6H_6$ requires C, 55·2; H, 5·4; N, 8·1%).

Reaction with semicarbazide. Griseofulvin (500 mg.) in pyridine (3 ml.) was treated with semicarbazide hydrochloride (176 mg.) in water (1 ml.). Dilution of the yellow solution after 24 hours afforded a brown solid separable into two fractions. (*a*) A dioxan-soluble fraction crystallised in needles, decomp. 240—242°, from aqueous dioxan [Found : C, 52·1; H, 4·9; N, 9·6; OMe, 21·6. $C_{18}H_{20}O_6N_3Cl$ requires C, 52·75; H, 4·9; N, 10·3; 3OMe, 22·7%]. This (*?*) *pyrazoline* was soluble in dilute mineral acids, and gave a wine-red colour with ferric chloride in methanol, discharged on addition of water. The Knorr pyrazoline test was negative. Hydrolysis by dilute hydrochloric acid at 40° for 5 minutes gave griseofulvic acid. (*b*) A dioxan-

insoluble fraction, decomp. 200—240°, on crystallisation from dilute acetic acid, afforded griseofulvin, m. p. 216—218° (mixed m. p. and analysis).

Griseofulvamine.—A suspension of griseofulvin (0·48 g.) in methanol (50 ml.) was saturated with dry ammonia for 1½ hours (complete solution). After 48 hours, excess of ammonia and solvent were removed *in vacuo* and the resultant *amine* (0·11 g.) crystallised from aqueous methanol in colourless needles, m. p. 264° (decomp.) (Found : C, 54·1, 54·1; H, 4·8, 4·6; Cl, 9·6; OMe, 19·0; Loss of wt. at 150°, 3·9. $C_{16}H_{16}O_5NCl,H_2O$ requires C, 54·0; H, 5·0; N, 3·95; Cl, 10·0; 2OMe, 17·4; H_2O, 5·05%). Ultra-violet absorption in methanol: $\lambda_{max.}$ 288, ~235 mμ; log ε 4·65, 4·09. The amine was soluble in dilute mineral acids; its acid solution, on warming, deposited griseofulvic acid. The amine was insoluble in cold dilute alkali, but dissolved when heated, with evolution of ammonia. It did not react with Brady's reagent. With ferric chloride in methanol, it gave a wine-red colour, discharged on addition of water. It slowly reduced ammoniacal silver nitrate at 100°.

The neutral N-*acetyl* derivative, prepared by reaction with acetic anhydride in pyridine, crystallised from ethanol in colourless silky needles, m. p. 247—248° depressed on admixture with griseofulvamine (Found : C, 56·7; H, 4·6; N, 3·8. $C_{18}H_{18}O_6NCl$ requires C, 56·8; H, 4·7; N, 3·7%). It gave a red precipitate with Brady's reagent, but no colour with ferric chloride.

Hydrolysis of Griseofulvin.—(a) *With ethanolic* N-*hydrochloric acid.* The method described by Oxford *et al.* (*loc. cit.*) gave griseofulvic acid as colourless prisms, decomp. 255—258° (from acetic acid), $[\alpha]_D^{17}$ +406° (*c*, 0·176 as sodium salt in water), $[\alpha]_D^{22}$ +399° (*c*, 1·004 as sodium salt in aqueous methanol) [Found : C, 56·5; H, 4·5; Cl, 10·1; OMe, 17·9%; *M* (Rast), 340; equiv. (potentiometric), 358. Calc. for $C_{16}H_{15}O_6Cl$: C, 56·7; H, 4·5; Cl, 10·5; 2OMe, 18·3%; *M*, 338·5]. Ultra-violet absorption max. : 326, 291, 267, 236 mμ (log ε 3·72, 4·40, 4·30, 4·17) in methanol; ~332, 289, 235 mμ (log ε 3·78, 4·70, 4·13) in 0·1N-sodium hydroxide. The p*K*, from the potentiometric titration curve (Fig. 5*a*), was 4·50, whence $K = 3·2 \times 10^{-5}$ at 18°. Griseofulvic acid gave only a pale orange colour with ferric chloride in methanol, but coupled readily with diazotised *o*-nitraniline. The Millon and the Gibbs reaction and the hydroxamic acid test (Feigl, " Spot Tests," Elsevier, New York, 3rd edn., 1947, p. 355) were negative. Hot ammonical silver and yellow mercuric oxide, but not Fehling's solution, were slowly reduced by griseofulvic acid.

(b) *With* 6N-*sulphuric acid.* Griseofulvic acid was obtained in 70% yield when griseofulvin was heated under reflux in a stream of nitrogen for 24 hours with 6N-sulphuric acid in an equal volume of ethanol.

(c) *With aqueous* 0·5N-*sodium hydroxide.* (i) In two experiments the hydrolysis proceeded as described by Oxford *et al.*, yielding decarboxygriseofulvic acid and norgriseofulvic acid. The former crystallised from ethanol in needles, m. p. 138°, $[\alpha]_D^{21}$ −29° (*c*, 1·00 in acetone) [Found : C, 61·2, 61·1; H, 5·1, 5·1; Cl, 11·5, 12·2; OMe, 19·9%; *M* (Rast), 283. Calc. for $C_{15}H_{15}O_4Cl$: C, 61·1; H, 5·1; Cl, 12·0; 2OMe, 21·0%; *M*, 294·6], and its 2 : 4-*dinitrophenylhydrazone* was obtained as red needles (from nitrobenzene), m. p. 242—244° (decomp.) (Found : C, 53·5; H, 3·9; N, 11·7. $C_{21}H_{19}O_7N_4Cl$ requires C, 53·3; H, 4·0; N, 11·8%). Norgriseofulvic acid formed needles, $[\alpha]_D^{18}$ +298° (*c*, 1·00 in acetone), m. p. 262° (decomp.), from methanol [Found : C, 55·6; H, 4·3; Cl, 11·1; OMe, 9·9, 9·45%; *M* (Rast), 310; equiv. (potentiometric), 158. Calc. for $C_{15}H_{13}O_6Cl$: C, 55·5; H, 4·0; Cl, 10·9; 1OMe, 9·6%; *M*, 324·6; equiv., 162 (dibasic acid)].

(ii) In all other experiments the reaction proceeded as follows : Powdered griseofulvin (5·0 g.) was heated under reflux with 0·5N-sodium hydroxide (750 ml.) for 5 hours. After cooling, the alkaline solution was filtered from the neutral solid (1·1 g.) and acidified, giving norgriseofulvic acid (2·8 g.). The neutral product, recrystallised twice from methanol (charcoal), gave needles, m. p. 148—159°, $[\alpha]_D^{20}$ −13° (*c*, 1·0 in acetone). A mixture with decarboxygriseofulvic acid of m. p. 138° melted at 138—158°. The product, m. p. 148—159°, sublimed without change in m. p. and gave the same dinitrophenylhydrazone as decarboxygriseofulvic acid of m. p. 138°. It was also obtained when the hydrolysis was carried out in an atmosphere of nitrogen although the reaction was much cleaner than in the presence of air. The neutral product, m. p. 148—159° (1·168 g.), in benzene (50 ml.) was adsorbed on alumina (12·5 × 1 cm.) activated at 150°/14 mm. for 3 hours. Decomposition appeared to be rapid on the column in ultra-violet light and to some extent in daylight. Adsorption, development, and elution were therefore carried out as quickly as possible in the dark. The following bands (from bottom to top) were obtained on development with benzene. First, a broad colourless band (grey-green fluorescence in ultra-violet light), which by elution with benzene and crystallisation from methanol gave decarboxy-

griseofulvic acid (880 mg.), m. p. 137°. The methanolic mother-liquors, on recovery, gave needles (125 mg.), m. p. 142—160°, unchanged by repeated crystallisation from methanol. Secondly, a narrow yellow band, from which elution with benzene and recovery afforded pale yellow prisms (80 mg.); after recrystallisation from xylene, this *substance* had m. p. 204—206° (with softening above 190°) (Found: C, 61·1; H, 5·2; Cl, 11·5; OMe, 20·1. $C_{15}H_{15}O_4Cl$ requires C, 61·1; H, 5·1; Cl, 12·0; 2OMe, 21·0%). The 2 : 4-dinitrophenylhydrazone crystallised from nitrobenzene in red needles, decomp. 216—218°. Finally, an orange band which, eluted with benzene +1% of ethanol, gave a red gum.

When decarboxygriseofulvic acid m. p. 134—137° (135 mg.), obtained as in (i), was adsorbed on alumina from a solution in benzene (20 ml.) as described above, the column consisted of one band only, namely the first. Elution and recovery yielded only decarboxygriseofulvic acid (120 mg.), colourless needles (from methanol), m. p. 136—137°.

iso*Griseofulvin*.—(*a*) Methylation of norgriseofulvic acid (90 mg.) with excess of ethereal diazomethane (Oxford *et al.*, *loc. cit.*) gave griseofulvin (40 mg.) and *iso*griseofulvin (30 mg.), long colourless needles (from ethanol), m. p. 200—201° (depressed below 180° on admixture with griseofulvin), $[\alpha]_D^{21}$ +215° (*c*, 1·3696 in acetone) (Found: C, 58·0; H, 5·0; Cl, 10·2; OMe, 25·6. Calc. for $C_{17}H_{17}O_6Cl$: C, 57·9; H, 4·85; Cl, 10·1; 3OMe, 26·4%).

(*b*) A suspension of griseofulvin (4 g.) in " AnalaR " methanol (270 ml.) was saturated with dry hydrogen chloride and then heated under reflux for 2 hours. Removal of most of the solvent *in vacuo* and pouring into ice-water afforded a precipitate which was collected and extracted with sodium carbonate solution. Acidification of the extract gave griseofulvic acid (1·3 g.). The dried neutral fraction (2·2 g.), crystallised from ethanol, gave *iso*griseofulvin (0·61 g.), m. p. 195—197°. The material recovered from the mother-liquor was chromatographed in benzene (40 ml.) on acid-washed alumina (pH 4, activated at 250° *in vacuo*). Gummy benzene-insoluble material was rejected. The column was eluted with ether containing 1% of methanol (fractions were collected in ultra-violet light). It yielded a narrow greyish band (evaporation gave a trace of oil), a purple band [evaporation gave *iso*griseofulvin (0·68 g.), m. p. 193—195°], and a violet-purple band [evaporation gave griseofulvin (0·33 g.), m. p. 210°].

Griseofulvic acid treated in the same way also gave *iso*griseofulvin and griseofulvin.

Contrary to the report by Oxford *et al.*, *iso*griseofulvin is much more soluble in most organic solvents than is griseofulvin. *iso*Griseofulvin did not yield carbonyl derivatives with Brady's reagent, *p*-nitrophenylhydrazine, hydroxylamine, or semicarbazide.

Hydrolysis of iso*Griseofulvin*.—*iso*Griseofulvin (0·5 g.) and N/8-sodium hydroxide (160 ml.) were heated to effect solution (30 minutes). Acidification afforded griseofulvic acid (0·41 g.), m. p. 256° (decomp.), $[\alpha]_D^{23}$ +388° (*c*, 0·4064 as sodium salt in aqueous methanol).

Hydrogenation of Griseofulvic Acid.—Griseofulvic acid (3·0 g.) in glacial acetic acid (600 ml.) was hydrogenated by shaking it with Adams's platinum oxide (250 mg.) at room temperature and pressure; uptake (3 mols.) was complete in 5 hours. The gum, obtained by evaporation of the filtered solution, was triturated with benzene (50 ml.), furnishing the *alcohol A* (27%), colourless needles (from aqueous methanol), m. p. 222—224°. It crystallised from chloroform and methanol with solvent of crystallisation, and had m. p. 120—140°, resetting and then melting 222—224°, $[\alpha]_D^{15}$ −37·5° (*c*, 1·00 in acetone) (Found: C, 56·2; H, 5·85; OMe, 17·0. $C_{16}H_{19}O_6Cl$ requires C, 56·1; H, 5·55; 2OMe, 18·0%).

After extraction with sodium carbonate and drying, the benzene mother-liquors were passed through a column of acid-washed (pH 4) alumina (16·5 × 1·5 cm.), activated at 240°/12 mm. for 3 hours. Development with benzene gave the following colourless bands, identified in ultra-violet light: (a) Upper broad band, fluorescing light blue; elution with benzene and recovery afforded *product C* (10%), colourless prisms (from aqueous methanol), m. p. 147—148° (Found: C, 61·8; H, 6·1; Cl, 11·8; OMe, 19·6. $C_{16}H_{19}O_4Cl$ requires C, 61·8; H, 6·1; Cl, 11·5; 2OMe, 20·0%). (b) Lower broad band, fluorescing dark blue; elution with benzene and recovery furnished the *alcohol B* (45%), colourless prisms (from aqueous methanol), m. p. 198—200° (Found: C, 58·6; H, 5·9; Cl, 11·0; OMe, 19·1. $C_{16}H_{19}O_5Cl$ requires C, 58·8; H, 5·8; Cl, 10·9; 2OMe, 19·0%). Further elution with benzene containing 1% ethanol afforded a lower broad band, fluorescing mauve, which, on elution with benzene–ethanol (99 : 1), gave a gum (200 mg.), and an upper broad band, with blue fluorescence, whence elution with the same solvent yielded A (3%), m. p. and mixed m. p. 222—224°.

Oxidation of Griseofulvic Acid Reduction Product B.—Product B (100 mg.) in acetic acid (2 ml.) was treated during 30 minutes with chromic oxide (100 mg.) in acetic acid (0·5 ml.) and water (0·2 ml.). After each addition, the mixture was heated on a water-bath until the oxidant had been consumed, and finally at 100° for 15 minutes, and then poured into water (10 ml.).

The precipitated *ketone* crystallised from ethyl acetate in platelets, m. p. 200—201°, depressed below 180° on admixture with starting material (Found : C, 59·1; H, 5·4; Cl, 10·5; OMe, 18·3. $C_{16}H_{17}O_5Cl$ requires C, 59·2; H, 5·2; Cl, 10·0; 2OMe, 19·0%). It was neutral to Universal indicator but slowly gave a yellow solution in dilute aqueous sodium hydroxide. It gave no colour with ferric chloride and did not react with Brady's reagent (see Part VI).

Potassium Hydroxide Fusion of Decarboxygriseofulvic Acid.—Decarboxygriseofulvic acid, m. p. 138° (80 mg.), was added to a melt of potassium hydroxide (0·5 g.) and water (0·1 ml.) at 250° and the bath-temperature raised to 280° (gas evolution and production of some tar). Acidification of an aqueous solution of the cooled melt afforded a brown precipitate which was taken up in ether and recovered. The resultant tar was sublimed at 80°/10^{-4} mm. Only a little colourless material sublimed, having m. p. 140° (decomp.) after softening at 80—90°. It did not contain halogen, was soluble in sodium hydrogen carbonate solution, and gave a brownish colour with ferric chloride. Orcinol readily sublimes under the above conditions. The tarry residue was intractable.

Pyrolysis of Griseofulvic Acid.—Griseofulvic acid, heated in a stream of nitrogen, readily evolved carbon dioxide (baryta) at the m. p. (250—260°). Extraction of the residue with chloroform and chromatography on alumina gave only amorphous products.

Similar results were obtained when griseofulvic acid was heated to its m. p. in " Dowtherm " or in synthetic quinoline.

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The Frythe, Welwyn Herts.
Imperial Chemical Industries Limited, Research Laboratories,
Hexagon House, Manchester, 9. [*Received, February 22nd,* 1952.]

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760. *Griseofulvin. Part II.* Oxidative Degradation.*

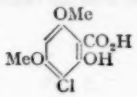
By John Frederick Grove, Doreen Ismay, J. MacMillan, T. P. C. Mulholland, and M. A. Thorold Rogers.

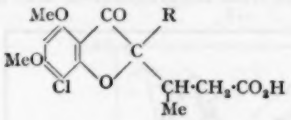
The observation by Oxford *et al.* (*Biochem. J.*, 1939, **33**, 240) that permanganate oxidation of griseofulvin and griseofulvic acid gave 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid and 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric acid (II; R = OH) has been confirmed and the former compound obtained on further permanganate oxidation of the latter. Oxidation of griseofulvic acid with alkaline hydrogen peroxide gives 7-chloro-4 : 6-dimethoxycoumaranone-2-β-butyric acid (II; R = H) from which (II; R = OH) is obtained on permanganate oxidation. Alkaline hydrolysis of (II; R = H) yields a dibasic acid, $C_{13}H_{13}O_6Cl$, and this same compound is also produced by oxidation of norgriseofulvic acid with alkaline hydrogen peroxide. Oxidation of griseofulvic acid with yellow mercuric oxide or of decarboxygriseofulvic acid with air under alkaline conditions results in the formation of a chlorohydroxydimethoxymethyldibenzofuran. 3-Methoxy-2 : 5-toluquinone is formed when griseofulvin but not *iso*griseofulvin or griseofulvic acid is oxidised with chromic oxide in acetic acid. The significance of these oxidation products in the general problem of the structure of griseofulvin is discussed.

By oxidation of griseofulvin in acetone with a large excess of potassium permanganate, Oxford, Raistrick, and Simonart (*Biochem. J.*, 1939, **33**, 240) obtained two monobasic acids which they considered to be 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic (I) and 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid (II; R = OH). Both acids were stated to be formed from griseofulvic acid under the same conditions, but decarboxygriseofulvic acid gave only the former. The structures of both these oxidation products

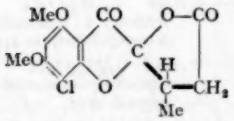
* Part I, preceding paper.

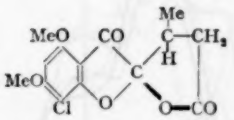
are considered to be correct for reasons which are discussed in Part III (following paper). It is sufficient to say here that we find, in agreement with Oxford *et al.*, that 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric acid readily undergoes lactonisation. Two isomeric lactones, $C_{14}H_{13}O_6Cl$, however, have been isolated. Lactone A, m. p. 220°, obtained by sublimation of (II; R = OH) *in vacuo* and presumably identical with the lactone, $C_{14}H_{13}O_6Cl$, m. p. 220°, described by Oxford *et al.* which they obtained by the action of acetic anhydride in pyridine on (II; R = OH), is apparently optically inactive. Using acetic anhydride–pyridine, we failed to isolate lactone A but obtained in its place lactone B, $C_{14}H_{13}O_6Cl$, m. p. 178—180°, $[\alpha]_D^{20}$ — 15·5°. Lactone B also results from the action of concentrated sulphuric acid on (II; R = OH). The two lactones are considered to be the diastereoisomers (III) and (IV); racemisation at $C_{(2)}$ of (II; R = OH) could occur *via* the open diketo-form during preparation or lactonisation.

(I) 



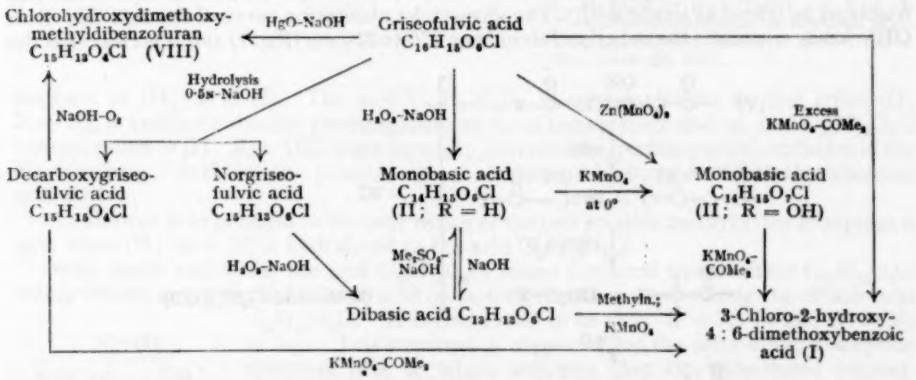
(II)

(III) 



(IV)

7-Chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric acid (II; R = OH), which gives 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (I) on further oxidation with permanganate, has been made in a variety of ways including the oxidation of griseofulvic acid with cold alkaline permanganate, hot chromic acid, or cold alkaline hypobromite. The lactone A sometimes accompanies or may replace the acid according to methods used in working up of the crude oxidation products. Only very small yields of 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric acid are obtained when the permanganate oxidation of griseofulvin is conducted as described by Oxford *et al.*, but the yield is very much improved (approx. 30%) by use of smaller quantities of zinc permanganate in neutral solution. Volatile acids are not produced in significant amounts during any of the oxidations with permanganate described above, nor are saturated dibasic acids.



A variety of new conditions for the oxidation of griseofulvin and its derivatives have been studied (see Scheme). The action of alkaline hydrogen peroxide on griseofulvic acid yielded a monobasic acid, $C_{14}H_{15}O_6Cl$, which closely resembles (II; R = OH) in its ultraviolet absorption spectrum (Fig. 1), but does not appear to have an alcoholic hydroxyl group, as judged by its infra-red spectrum. This acid is rapidly oxidised by ice-cold

alkaline permanganate to (II; R = OH) and is therefore considered to be 7-chloro-4 : 6-dimethoxycoumaranone-2-β-butyric acid (II; R = H); it is in fact an intermediate in the formation of the acid (II; R = OH) by permanganate oxidation of griseofulvin and is present in small quantities in the products. This has not been shown directly owing to difficulty in the separation of the two acids by fractional crystallisation but alkaline hydrolysis of the crude oxidation product (see Part III, following paper) gives, in very low yield, the dibasic acid $C_{13}H_{13}O_6Cl$ (see below) which results from alkaline hydrolysis of (II; R = H).

Oxidation of the dibasic norgriseofulvic acid, $C_{15}H_{13}O_6Cl$, both by hydrogen peroxide and by ice-cold alkaline permanganate gives a new dibasic acid, $C_{13}H_{13}O_6Cl$, containing one methoxyl group. This acid can be made by hydrolysis of 7-chloro-4 : 6-dimethoxycoumaranone-2-β-butyric acid by alkali in an atmosphere of nitrogen. The fragment C_2 has been lost from norgriseofulvic acid and this is the same loss as takes place in the

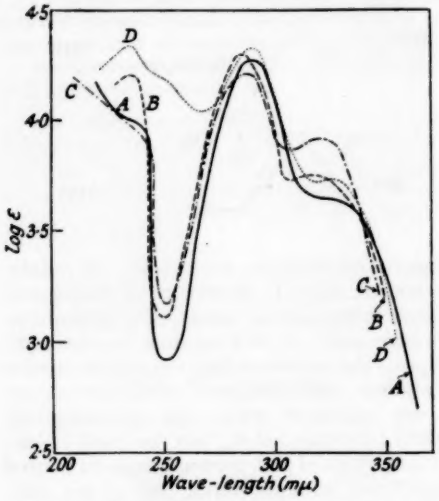


FIG. 1.

A, ——— *Acid* $C_{14}H_{15}O_7Cl$. *7-Chloro-2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid.*

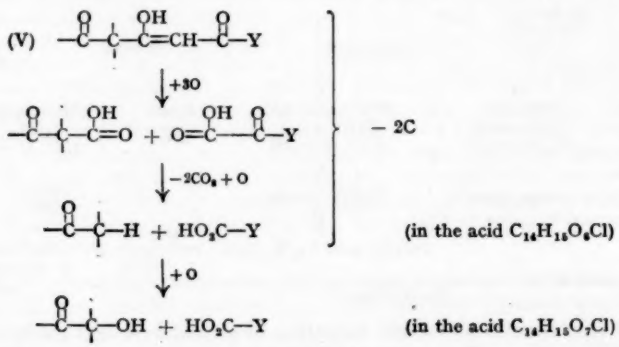
B, – – – – – *Acid* $C_{14}H_{15}O_6Cl$. *7-Chloro-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid.*

C, · — · — *Acid* $C_{13}H_{13}O_6Cl$. *7-Chloro-4(or 6)-hydroxy-6(or 4)-methoxycoumaran-3-one-2-β-butyric acid.*

D, · · · · · · · *Griseofulvin.*

(*All in methanol.*)

analogous conversion of griseofulvic acid into (II; R = H). In neither case could this fragment be traced as oxalic acid. The ultra-violet absorption curve of the acid (II; R = OH) closely resembles that of griseofulvin from 270 to 350 mμ (Fig. 1) and it is clear that the



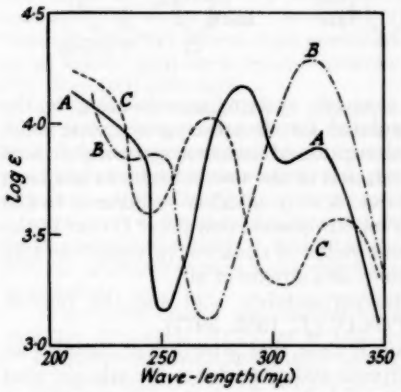
main chromophoric system of the latter compound is unaffected by the oxidation. It follows that the β-diketone grouping, believed to be present (Part I), must have undergone degradation and, if griseofulvic acid contained the partial structure (V), two molecules of

carbon dioxide could be lost—one each from the intermediate β-keto-acid and α-keto-acid groupings, for a total addition of 4 oxygen atoms, leaving a net loss of C_2.

Similar considerations apply to the oxidation of the dibasic norgriseofulvic acid to the dibasic acid $C_{13}H_{13}O_6Cl$. The ultra-violet absorption of the latter compound in methanol (Fig. 1) does not differ greatly from that of (II; R = OH) and it is clear that in this case also the β-diketone grouping undergoes oxidation. It also follows that the phenolic nucleus of norgriseofulvic acid (see Part I) is unaffected and that the second acid group in the compound $C_{13}H_{13}O_6Cl$ is the strongly acidic phenolic hydroxyl group believed to be present in norgriseofulvic acid.

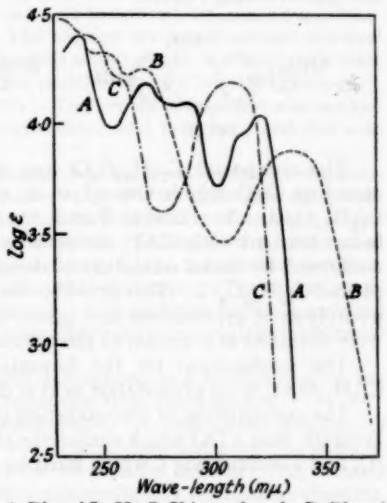
Like norgriseofulvic acid, the acid $C_{13}H_{13}O_6Cl$ shows some phenolic properties, and the ultra-violet absorption curve shows a marked shift to longer wave-lengths in 0·1N-sodium hydroxide (Fig. 2). Furthermore, the acid $C_{13}H_{13}O_6Cl$ can be remethylated with methyl

FIG. 2.



A, Acid $C_{13}H_{13}O_6Cl$ *in methanol. B, Acid* $C_{13}H_{13}O_6Cl$ *in* 0·1N-NaOH. *C, Acetate* $C_{15}H_{13}O_6Cl$ *in methanol.*

FIG. 3.

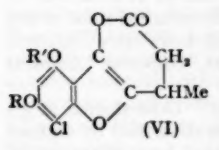


A, Phenol $C_{15}H_{13}O_4Cl$ *in methanol. B, Phenol* $C_{15}H_{13}O_4Cl$ *in* 0·1N-NaOH. *C,* 3 : 4 : 7-*Trimethoxydibenzofuran in methanol* (Tarbell, Frank, and Fanta, *J. Amer. Chem. Soc.*, 1946, **68**, 502).

sulphate to (II; R = H). The acid $C_{13}H_{13}O_6Cl$, in contrast to its methyl ether (II; R = H), is stable to alkaline permanganate at room temperature and an acid $C_{13}H_{13}O_7Cl$ corresponding to (II; R = OH) is not formed; nevertheless, permanganate oxidation of the diazomethane methylation product gives 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (I).

An attempt is in progress to discover which of the two possible methyl ether groupings is split when (II; R = H) is hydrolysed to the acid $C_{13}H_{13}O_6Cl$.

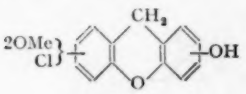
With acetic anhydride the acid $C_{13}H_{13}O_6Cl$ forms a neutral monoacetate $C_{15}H_{13}O_6Cl$ which titrates as a potential tribasic acid on lactone titration, regenerating the dibasic acid $C_{13}H_{13}O_6Cl$. It is considered to be (VI; R = Ac or Me, R′ = Me or Ac). This structure is supported by the ultra-violet absorption spectrum (Fig. 2) which indicates that the substituted coumaranone chromophore is no longer present and resembles the type of spectrum found with some compounds in which an ethylenic bond is conjugated with an aromatic nucleus [*e.g.*, the (—)-methoxyacetate of (±)-tetrahydrocannabinol (Russell *et al.*, *J.*, 1941, 826)]; the infra-red spectrum is in agreement with this view.



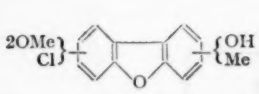
(VI)

Griseofulvin is stable to the action of potassium dichromate in acetic acid but is readily oxidised by chromic oxide to 3-methoxy-2 : 5-toluquinone (XI). This is not obtained when *iso*griseofulvin is oxidised with chromic oxide under the same conditions.

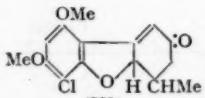
Griseofulvic acid is oxidised by alkaline yellow mercuric oxide to a dimethoxy-phenol, $C_{15}H_{13}O_4Cl$, the methyl ether of which is fully stable to permanganate in acetone and contains no ethylenic linkages on hydrogenation. The compound $C_{15}H_{13}O_4Cl$ is therefore aromatic and, accordingly, is optically inactive. It has no carbonyl reactivity and the infra-red spectrum confirms the absence of keto-groups. The fourth oxygen atom must therefore be present in an ether linkage and it follows that the compound contains three fused rings. Of the structures admissible from fundamental considerations, only the substituted dibenzopyran (VII) or dibenzofuran (VIII) need be considered and of these the ultra-violet absorption spectrum (Fig. 3) is consistent only with (VIII). Moreover, Kühn-Roth oxidations of the phenol $C_{15}H_{13}O_4Cl$ and its methyl ether show the presence of one *C*-methyl group, favouring (VIII).



(VII)



(VIII)

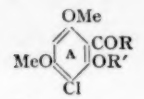


(IX)

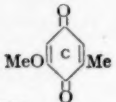
The compound $C_{15}H_{13}O_4Cl$ has, in fact, the aromatic system corresponding to the structure (IX) which Oxford *et al.* (*loc. cit.*) postulated for decarboxygriseofulvic acid, $C_{15}H_{15}O_4Cl$. As stated in Part I, the ultra-violet absorption of decarboxygriseofulvic acid is inconsistent with (IX); nevertheless, the close relation of the two substances has been confirmed by aerial oxidation of decarboxygriseofulvic acid in alkaline suspension to the phenol $C_{15}H_{13}O_4Cl$. This provides the explanation for our observation (Part I) that in the hydrolysis of griseofulvin and griseofulvic acid, good yields of decarboxygriseofulvic acid were obtained in a stream of nitrogen and less, or none, in a stream of air.

The mechanisms for the formation of decarboxygriseofulvic acid and the phenol, $C_{15}H_{13}O_4Cl$, from griseofulvic acid is discussed in Part IV (*J.*, 1952, 3977).

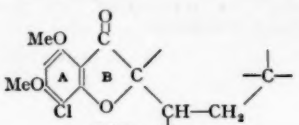
The constitution of the oxidation products makes it clear that griseofulvin contains an aromatic ring A (X) which carries the chlorine substituent and gives rise to the salicylic acid (I), and a second ring C which must be hydroaromatic and gives rise to the quinone (XI).



(X)



(XI)



(XII)

The carbon skeleton of griseofulvin has been shown (Part I) to be stable under acid conditions; it is unlikely, therefore, that any molecular rearrangement is involved in the formation of (XI). The similarity in the ultra-violet absorption of griseofulvin and 7-chloro-4 : 6-dimethoxycoumaranone-2-β-butyric acid also suggests that griseofulvin contains the substituted coumaranone ring system (XII).

Experimental

M. p.s are corrected. The infra-red spectra of solid samples were obtained as described in Part I. Microanalyses are by Drs. Strauss and Weiler, Oxford (who also determined some of the ultra-violet absorption spectra), by Mr. W. Brown, Imperial Chemical Industries Limited, Butterwick Research Laboratories, and by the Analytical Department, Imperial Chemical Industries Limited, Dyestuffs Division.

Permanganate Oxidation of Griseofulvin.—(a) *Potassium permanganate.* Griseofulvin (4 g.) was oxidised with potassium permanganate (16·0 g., 13·5 O) in the manner described by Oxford *et al.* (*loc. cit.*). 3-Chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid was purified by sublimation at 160°/2 × 10^{-3} mm., followed by crystallisation from ethyl acetate, giving colourless needles

(104 mg.), m. p. 221—222° (decomp.) [Found: C, 46·5; H, 3·85; Cl, 14·65; OMe, 25·35%; *M* (Rast), 252. Calc. for $C_9H_9O_5Cl$: C, 46·45; H, 3·9; Cl, 15·25; 2OMe, 26·7%; *M*, 232·5]. The m. p. was found to vary between 200° and 222° (decomp.) depending on crystal size and rate of heating. It was confirmed that the acid, which gave a negative Millon but positive Gibbs reaction, was methylated by methanolic diazomethane to methyl 3-chloro-2 : 4 : 6-trimethoxybenzoate, identified by analysis and comparison with a synthetic specimen (Calam and Oxford, *J.*, 1939, 280).

7-Chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric acid (II; R = OH) was purified by crystallisation from ethyl methyl ketone–light petroleum (b. p. 60—80°) (charcoal), affording colourless needles (95 mg.), m. p. 198° (decomp.) (Found: C, 51·0; H, 4·7%; equiv., 323. Calc. for $C_{13}H_{14}O_6Cl{\cdot}CO_2H$: C, 50·8; H, 4·6%; equiv., 330·5). No volatile acids or saturated dibasic acids were detected in the ultimate acetone mother-liquors.

(b) *Zinc permanganate.* Griseofulvin (4·0 g.) in pure acetone (1300 ml.) was treated with a 1·9% aqueous solution of zinc permanganate (483 ml., 8O) at room temperature with shaking at 15-minutes' intervals. After 2·5 hours, the brown precipitate was collected and washed with acetone. The filtrate and washings were concentrated *in vacuo* to 300 ml. whereupon a colourless solid separated which was extracted with ether. The sodium carbonate-washed ethereal extract yielded unchanged griseofulvin (140 mg.); ether-extraction of the acidified carbonate washings gave the acid (II; R = OH) (1·1 g.), colourless needles, m. p. 178—186° (decomp.), from ethyl methyl ketone–light petroleum (b.p. 60—80°). The brown precipitate was worked up as before, yielding 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (180 mg.) and the acid (II; R = OH) (100 mg.).

(c) *Search for volatile acids.* The aqueous acetone mother-liquors, from treatment of griseofulvin (4·0 g.) in acetone (1300 ml.) with zinc permanganate (7·0 g., 6O) in water (400 ml.), were made slightly alkaline by sodium carbonate and concentrated to 300 ml. Recovery of the precipitated solid by ether-extraction gave unchanged griseofulvin (200 mg.), m. p. and mixed m. p. 214—216°. Acidification of the sodium carbonate solution to Congo-red afforded 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (40 mg.), m. p. 222—224° (decomp.). The acid mother-liquors were steam-distilled, and 50 ml. of distillate collected. Although the distillate required 3·00 ml. of 0·112N-sodium hydroxide for neutralisation (phenolphthalein), no volatile acids could be isolated.

Ether-extraction of the residual solution after steam-distillation, and recovery, gave the acid (II; R = OH) (1·1 g.), m. p. 185—189° after crystallisation from ethyl acetate.

Oxidation of Griseofulvic Acid with Potassium Permanganate.—A well-stirred solution of griseofulvic acid (1·0 g.) in sodium carbonate (20 ml.) was treated dropwise with 1% aqueous potassium permanganate until the pink colour persisted for 15 minutes (310 ml., 10O). After removal of manganese dioxide by filtration, the acidified mother-liquors were steam-distilled. The distillate required only 2·4 ml. of 0·1N-sodium hydroxide for neutralisation, and attempts to isolate volatile acids were unsuccessful. The residual solution from the steam-distillation was concentrated to 200 ml. and extracted in turn as follows. (*a*) Ether (100 ml.) removed an amorphous solid which sublimed at 170°/10^{-4} mm. Dissolution of the yellow sublimate in ether, extraction with sodium hydrogen carbonate, and recovery afforded a colourless solid, crystallising from ethanol in needles (30 mg.), m. p. 200—210°, identified by the infra-red spectrum as lactone A (see below). The gum obtained by acidification of the bicarbonate extract was worked up with a similar fraction obtained in (*b*) below.

(*b*) Ethyl acetate (2 × 200 ml.) yielded a brown gum, which on sublimation at 10^{-4} mm. gave (i) a yellow gum at 140°, and (ii) a yellow solid at 170°. The former crystallised from ethanol in colourless needles (20 mg.), m. p. 218—220°, of lactone A (see below) (Found: C, 53·4; H, 4·4; Cl, 10·7. Calc. for $C_{14}H_{13}O_6Cl$: C, 53·7; H, 4·2; Cl, 11·3%), absorption max. in methanol at 328, 290, and ~236 mμ (log ε 3·61, 4·20, 4·20). Dissolution of fraction (ii) in ether and treatment as in (*a*) afforded the lactone A, m. p. 210—220°, and a yellow oil. The latter, combined with the corresponding fraction in (*a*), crystallised from ethyl methyl ketone–light petroleum (b. p. 40—60°) in colourless needles, m. p. 180° (decomp.), identified as the acid (II; R = OH) by the infra-red spectrum. (*c*) Continuous extraction (24 hours) with hot ethyl acetate, sublimation of the recovered material at 140°/10^{-4} mm., dissolution of the sublimate in ether, washing with water, and recovery afforded a sticky material from which a colourless solid (1 mg.), m. p. 160° (decomp.), was obtained on a porous plate. This acid differed from the acid (II; R = OH) by its greater solubility in water and by its dissolving to a colourless solution in bicarbonate.

Lactonisation of 7-Chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric Acid (II; R =

OH).—(a) *By sublimation.* Sublimation of the acid (100 mg.) at 180°/10^{-4} mm., followed by extraction of the sublimate with sodium carbonate (43 mg. recovery of acid), afforded a lactone, colourless needles (30 mg.), m. p. 218—222°, from ethanol. This lactone (now called lactone A) corresponds to the lactone, m. p. 222°, described by Oxford *et al.* (*loc. cit.*). Although neutral to litmus and Universal indicator in aqueous suspension, it slowly dissolved in sodium hydroxide and sodium hydrogen carbonate solutions, giving yellow solutions.

Lactone A appeared to be optically inactive, $[\alpha]_D^{18} \gtrless \pm 3°$ (*c*, 1·10 in acetone; *l*, 1 dm.). Treatment with excess of 0·1N-sodium hydroxide for 30 minutes at 100° and back-titration gave an apparent equivalent of 343 (Calc. for $C_{14}H_{13}O_6Cl$: 312·5). Acidification of the solution to Congo-red and recovery in ether gave lactone A, m. p. 218—220°, and not (II; R = OH).

(b) *With acetic anhydride.* Treatment of the acid (II; R = OH) (150 mg.) in dry pyridine (1·5 ml.) with acetic anhydride (0·6 ml.) at 35° for 4 days and pouring the reaction mixture into ice-water and dilute hydrochloric acid gave a colourless solid which was taken up in benzene and extracted with sodium carbonate solution. The dried benzene extract was chromatographed on alumina (5 × 0·5 cm.) (pH 4; activated at 150°). Elution of a band fluorescing vivid violet in ultra-violet light with benzene (15 ml.) afforded lactone B, $C_{14}H_{13}O_6Cl$, colourless needles (95 mg.) (from ethanol), m. p. 163°, which resolidified and then remelted at 178—180° (Found: C, 53·4; H, 4·2; Cl, 10·8; OMe, 19·2. $C_{14}H_{13}O_6Cl$ requires C, 53·7; H, 4·2; Cl, 11·3; 2OMe, 19·8%). The m. p. of lactone B was not raised by vacuum-sublimation followed by repeated crystallisation from ethanol. Seeding with lactone A yielded a small crop of crystals, m. p. 195°, not raised by further crystallisation. A mixture of lactones A and B melted indefinitely between 180—210°. Lactone B, like lactone A, was insoluble in cold sodium hydroxide and sodium carbonate but dissolved slowly when kept or warmed, giving yellow solutions from which the colour was discharged by acidification. The infra-red spectra of the two lactones were very similar but not completely identical; lactone A showed a band at 1150 cm.$^{-1}$ absent from the spectrum of lactone B. The latter showed a " shoulder " at 1125 cm.$^{-1}$ absent from the former.

(c) *With sulphuric acid.* The orange solution obtained on keeping the acid (50 mg.) overnight in concentrated sulphuric acid (0·5 ml.) was poured over crushed ice. The yellow solid (37 mg.), after being washed with sodium carbonate and water, was sublimed at 190°/10^{-4} mm. and the yellow sublimate crystallised from ethanol. Colourless needles, m. p. and mixed m. p. with lactone B, 180—182°, were separated by hand-picking from colourless needles, m. p. 182—190°, which are considered to be a mixture of lactones A and B.

Permanganate Oxidation of Decarboxygriseofulvic Acid.—The brown precipitate, obtained by treatment of decarboxygriseofulvic acid (500 mg.) in pure acetone (10 ml.) with potassium permanganate (2·0 g.) in acetone (100 ml.) for 5 hours, was ground with dilute aqueous ammonia and worked up as described by Oxford *et al.* The product crystallised in needles (175 mg.), m. p. 196° (decomp.), from ethyl acetate after sublimation at 160°/10^{-3} mm. and was identified as 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid by mixed m. p., infra-red spectrum, and *X*-ray diffraction pattern.

Potassium Permanganate Oxidation of the Acid (II; R = OH).—The acid (100 mg.) in acetone (5 ml.) was treated with potassium permanganate (400 mg.) in acetone (20 ml.) and kept for 24 hours at room temperature with occasional shaking. The brown precipitate was worked up in the usual way, affording 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (50 mg.), m. p. 218—222°, identified by mixed m. p., infra-red absorption spectrum, and *X*-ray powder diffraction. The aqueous acid filtrate slowly deposited unchanged starting material (20 mg.), m. p. and mixed m. p., 188—190° (decomp.).

Oxidation of Griseofulvic Acid with Hydrogen Peroxide.—Griseofulvic acid (1·0 g.) in 0·1N-sodium hydroxide (125 ml.) was treated with 30% hydrogen peroxide (25 ml.) and, after 2 days at room temperature with occasional stirring, a further 20 ml. of 0·1N-sodium hydroxide were added. At the end of the fourth day, the solid obtained by acidification was extracted (10 minutes) with boiling toluene, leaving unchanged griseofulvic acid, m. p. 240—244° (decomp.) (270 mg.). Concentration of the toluene extract furnished *7-chloro-4 : 6-dimethoxycoumaranone-2-β-butyric acid* (II; R = H) which crystallised from toluene in colourless prisms (500 mg.), m. p. 152—154°, $[\alpha]_D^{20}$ −38·7° (*c*, 1·627 in methanol) (Found: C, 53·9, 54·05; H, 4·95, 4·9; Cl, 11·1, 10·5; OMe, 19·05, 18·65%; equiv., 320. $C_{13}H_{14}O_4Cl{\cdot}CO_2H$ requires C, 53·45; H, 4·75; Cl, 11·3; 2OMe, 19·7%; equiv., 314·5), ultra-violet absorption max. in methanol at 321, 286, and 236 mμ (log ε 3·73, 4·33, 4·23). The acid (II; R = H) showed no reducing properties, did not form a dinitrophenylhydrazone with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, and reacted only slowly with bromine in carbon tetrachloride. It gave no colour with ferric chloride, and the Millon reaction was negative.

Permanganate Oxidation of 7-Chloro-4 : 6-dimethoxycoumaranone-2-β-butyric Acid (II; R = H).—To an ice-cold solution of the acid (160 mg.) in N-sodium carbonate (10 ml.) a solution of potassium permanganate (0·455 g.) in water (10 ml.) was added dropwise and with stirring, during 1½ hours, a permanent pink colour being then obtained (3—4 ml., 3O). Decolorisation with sulphur dioxide and acidification left a crystalline solid (40 mg.) which was combined with a further fraction (40 mg.), obtained on concentration of the mother-liquors *in vacuo*, and crystallised from ethyl methyl ketone–light petroleum (b. p. 60—80°); it had m. p. and mixed m. p. with (II; R = OH), 204·5° (decomp.).

Alkaline Hydrolysis of 7-Chloro-4 : 6-dimethoxycoumaranone-2-β-butyric Acid.—The acid (350 mg.) in 3N-sodium hydroxide (10 ml.) was heated under reflux for 5 hours in a slow stream of nitrogen. The acidified solution, on being kept for 24 hours at 0°, deposited a colourless solid (200 mg.), m. p. 194—198° (decomp.). Recrystallisation twice from ethyl acetate afforded plates, m. p. 210·5—214° (decomp.), of 7-chloro-4(or 6)-hydroxy-6(or 4)-methoxycoumaranone-2-β-butyric acid, $[\alpha]_D^{18}$ −71° (*c*, 1·10 in methanol) [Found : C, 51·65, 51·65; H, 4·45, 4·5; Cl, 11·55; OMe, 10·4%; equiv., 162·5; $C_{13}H_{13}O_6Cl$ requires C, 51·9; H, 4·3; Cl, 11·8; 1OMe, 10·3%; equiv., 150 (dibasic acid)]. Ultra-violet absorption max. : 321, 289, ~242 mμ (log ε 3·91, 4·20, 3·92) in methanol; 320, 250 mμ (log ε 4·32, 3·89) in 0·1N-sodium hydroxide. The dibasic acid $C_{13}H_{13}O_6Cl$ gave a positive Millon reaction and a red-brown colour with ferric chloride and showed weak but positive coupling with diazotised amines. It showed no reducing properties and did not react with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid.

Methylation of the acid $C_{13}H_{13}O_6Cl$ (30 mg.) with methyl sulphate and 10% sodium hydroxide in the usual way afforded a white solid which crystallised from toluene in prisms, m. p. 146—149° (7 mg.), identified as the acid (II; R = H) by comparison of the infra-red spectra.

The acid $C_{13}H_{13}O_6Cl$ (100 mg.) and acetic anhydride (1·5 ml.) were heated under reflux for 30 minutes and the cooled solution was poured on crushed ice. The resultant neutral *monoacetyl* compound crystallised from ethanol in needles, (70 mg.) m. p. 197—198° [Found : C, 55·6, 55·8; H, 4·2, 4·1; Cl, 10·6; OMe, 10·6; Ac, 18·8%; *M* (Rast), 292. $C_{15}H_{13}O_6Cl$ requires C, 55·5; H, 4·0; Cl, 10·9; 1OMe, 9·6; 1Ac, 13·3%; *M*, 324). Ultra-violet absorption max : 332, 272, ~229 mμ (log ε 3·62, 4·07, 4·19) in methanol. The infra-red spectrum showed a single intense band in the >C=O region at 1774 cm.$^{-1}$ and a weak band at 1652 cm.$^{-1}$ attributed to the ethylenic bond. The 1774 cm.$^{-1}$ band is consistent with the presence of phenyl or vinyl ester (or lactone) groupings (Grove and Willis, *J.*, 1951, 877; Grove, *J.*, 1951, 883) and its strength explained by the presence of two such groupings in the molecule. The acetate which showed an intense fluorescence in ultra-violet light was insoluble in potassium hydrogen carbonate solution but dissolved slowly in warm sodium hydroxide.

The acetate (30·5 mg.) was heated on a water-bath for 45 minutes with 0·121N-sodium hydroxide (5·80 ml.). Back-titration with 0·121N-hydrochloric acid required 3·80 ml., giving an apparent equivalent of 105 ($C_{15}H_{13}O_6Cl$ requires equiv. 108 as a potential tribasic acid). The solution, made strongly acid with concentrated hydrochloric acid and concentrated, yielded the dibasic acid $C_{13}H_{13}O_6Cl$, identified by mixed m. p. and infra-red spectrum.

The acetate gave no colour with ferric chloride and a negative Millon reaction. When heated with an equal weight of *p*-toluidine for 1 hour on the steam-bath it gave the *monotoluidide*, m. p. 223—225° (from aqueous methanol), of the acid $C_{13}H_{13}O_6Cl$ (Found : C, 61·95; H, 5·2; N, 4·2; Cl, 8·6. $C_{20}H_{20}O_5NCl$ requires C, 61·6; H, 5·15; N, 3·6; Cl, 9·1%). This was insoluble in cold aqueous sodium hydrogen carbonate and sodium carbonate, but soluble in sodium hydroxide solution.

Oxidation of Norgriseofulvic Acid to the Acid $C_{13}H_{13}O_6Cl$.—(a) *Hydrogen peroxide.* Norgriseofulvic acid (400 mg.) in N-potassium hydroxide (5·2 ml.) and water (20·8 ml.) was treated with 30% hydrogen peroxide (5 ml.). After 24 hours the faintly purple solution was acidified and cooled in ice; the deposited solid crystallised from ethyl acetate in colourless plates (130 mg.), m. p. and mixed m. p. with the dibasic acid, $C_{13}H_{13}O_6Cl$, 211—213°.

(b) *Potassium permanganate.* To a well-stirred solution of norgriseofulvic acid (250 mg.) in N-sodium carbonate (15 ml.) at 0°, a solution of potassium permanganate (0·081 g./ml., 1O/ml.) was added dropwise until oxidation was complete (10—11 ml.). Decolorisation with sulphur dioxide, followed by acidification, extraction with ether, and recovery, gave a gum crystallising in prisms (from benzene–ethyl acetate), m. p. 202—206° (decomp.), identified as the acid $C_{13}H_{13}O_6Cl$ by mixed m. p. and comparison of the infra-red spectra.

Oxidation of Griseofulvic Acid with Yellow Mercuric Oxide.—A mixture of griseofulvic acid (1·8 g.), 2N-sodium hydroxide (5·25 ml.), water (12·9 ml.), and yellow mercuric oxide (2·5 g.) was stirred on a steam-bath for 18 hours (rapid darkening and finally production of some

metallic mercury). To the grey suspension was added saturated sodium chloride solution (25 ml.), and the precipitate removed (centrifuge; washing with water). Acidification of the alkaline mother-liquors gave unchanged griseofulvic acid (500 mg.), m. p. 226—228°. The dark precipitate, suspended in N-hydrochloric acid (10 ml.), was treated with hydrogen sulphide for 7 hours at 50—60° and thereafter for 11 hours at room temperature. Extraction (Soxhlet) of the washed precipitate with methanol furnished a brown solid which crystallised (charcoal) from toluene in fine colourless needles (500 mg.), m. p. 199° [Found: C, 61·5; H, 4·75; Cl, 12·45; OMe, 20·65; *C*-Me (Kühn–Roth), 6·4. $C_{15}H_{13}O_4Cl$ requires C, 61·5; H, 4·5; Cl, 12·3; 2OMe, 21·2; 1*C*-Me, 5·1%]. Ultra-violet absorption max.: 320, 310, 286, 268, 238 mμ (log ε 4·04, 3·94, 4·10, 4·18, 4·40) in methanol; 335, 268, 252 mμ (log ε 3·88, 4·28, 4·32) in 0·1N-sodium hydroxide. The infra-red spectrum showed a strong –OH absorption at 3255 cm.$^{-1}$ and the absence of carbonyl groups. The *phenol*, which was optically inactive, dissolved in hot 2N-sodium hydroxide from which the sodium salt crystallised on cooling. The phenol coupled readily with diazonium salts although both Millon and Gibbs reactions were negative. It was unsaturated to potassium permanganate and absorbed bromine in chloroform solution with evolution of hydrobromic acid. The *picrate* formed brick-red needles, m. p. 196—198°, from aqueous ethanol (Found: C, 47·95; H, 3·2; N, 8·7; Cl, 7·4. $C_{21}H_{16}O_{11}N_3Cl$ requires C, 47·8; H, 3·05; N, 8·05; Cl, 6·8%); the *toluene-p-sulphonyl* derivative crystallised in colourless prisms, m. p. 196°, from ethyl acetate (Found: C, 58·1; H, 4·15: $C_{22}H_{19}O_6ClS$ requires C, 59·1; H, 4·25%).

The phenol was also formed by oxidation of griseofulvin by alkaline yellow mercuric oxide.

The *methyl ether*, obtained by treatment with methyl sulphate and alkali, crystallised in flat needles from ethanol (charcoal), and hexagonal prisms from aqueous acetone, and had m. p. 168—170° (Found: C, 62·35; H, 4·85; OMe, 29·9; *C*-Me, 5·9. $C_{16}H_{15}O_4Cl$ requires C, 62·65; H, 4·9; 3OMe, 30·35; 1*C*-Me, 4·9%.) It was optically inactive and was stable to permanganate in acetone.

Chromic Oxide Oxidations.—(a) *Griseofulvin.* Griseofulvin (1·0 g.) in warm acetic acid (15 ml.) was treated dropwise with chromic oxide (3·0 g.) in acetic acid (15 ml.) and water (6 ml.), whereupon a vigorous reaction set in. After spontaneous refluxing (10 minutes), the solution was heated under reflux for 30 minutes, diluted with water, and extracted with benzene. Recovery and sublimation at 90°/10^{-4} mm. gave 3-methoxy-2 : 5-toluquinone, long yellow needles (130 mg.), m. p. 148—150°, from methanol, identified by analysis and mixed m. p. with a specimen synthesised as described by Henrich and Nachtigall (*Ber.*, 1903, **36**, 889). Crystallisation of the residue from ethanol gave unchanged griseofulvin (34 mg.), m. p. 217—218°.

(b) iso*Griseofulvin.* Oxidation as in (*a*) gave a small amount of yellow intractable oil, devoid of ketonic properties and partly soluble in sodium hydroxide, and a little unchanged *iso*griseofulvin.

(c) *Griseofulvic acid.* This (250 mg.) was oxidised with chromium trioxide (750 mg.) as in (*a*). Benzene extraction of the diluted reaction mixture yielded a gum which crystallised from methanol in colourless needles, m. p. 194—195°, identified as lactone A of the acid $C_{14}H_{15}O_7Cl$ by mixed m. p. and infra-red spectroscopy. The m. p. could not be raised by crystallisation or sublimation.

Hypobromite Oxidation of Griseofulvic Acid.—Griseofulvic acid (160 mg.) in 2·5 N-sodium hydroxide (2 ml.) was treated with 2 ml. of a solution containing 6·5 g. of bromine in 35 ml. of solution. After 1 hour, the liberated bromoform was separated and excess of hypobromite removed with sulphur dioxide. Acidification afforded an orange gum which solidified during 24 hours at 0°. After filtration and extraction with toluene, the toluene-insoluble fraction (35 mg.) was crystallised from ethyl methyl ketone–light petroleum in colourless needles, m. p. 180° (decomp.), identified as the acid (II; R = OH) by a mixed m. p. and infra-red absorption spectrum. Evaporation of the toluene left a gummy solid which was intractable, but which, from its behaviour, probably contained some of the acid (II; R = H).

Aerial Oxidation of Decarboxygriseofulvic Acid.—Decarboxygriseofulvic acid (110 mg.) and 2N-sodium hydroxide (17 ml.) were heated under reflux while a slow stream of air was passed through the solution. At the end of 3 hours some solid material remained undissolved. Crystalline material which separated on cooling was dissolved by the addition of water, and the solution filtered. Concentration of the filtrate *in vacuo* and dilution with an equal volume of a saturated solution of sodium chloride afforded a crystalline solid which was collected (centrifuge) and dissolved in water. Acidification of the aqueous solution yielded a solid which crystallised from toluene in long felted needles, m. p. 198—201° (8 mg.), identified as the phenol $C_{15}H_{13}O_4Cl$ by comparison of the infra-red and ultra-violet absorption spectra.

Oxidation of the Acid $C_{13}H_{13}O_6Cl$.—(a) The acid $C_{13}H_{13}O_6Cl$ (120 mg.) in 2N-sodium carbonate (1 ml.) and water (5 ml.) was recovered unchanged after treatment with potassium permanganate (1·0 g.) in water (25 ml.) at room temperature.

(b) *After methylation.* The acid (400 mg.) in methanol (10 ml.) was treated with excess of ethereal diazomethane and the product, without purification, was directly oxidised by heating its acetone solution (40 ml.) under reflux for 16 hours with powdered potassium permanganate. The resultant solid was shaken with 2N-ammonia solution for 2 hours. Acidification of the filtrate gave 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (100 mg.), m. p. 206—208°, identified by comparison of the *X*-ray diffraction patterns.

We are indebted to Mr. H. A. Willis, Imperial Chemical Industries Limited, Plastics Division, for infra-red spectrographic facilities and to Dr. A. Spinks and Mr. M. St. C. Flett who obtained some of the ultra-violet and infra-red spectra.

Imperial Chemical Industries Limited, Butterwick Research Laboratories, The Frythe, Welwyn, Herts.
Imperial Chemical Industries Limited, Research Laboratories, Hexagon House, Manchester, 9. [*Received, February 22nd*, 1952.]

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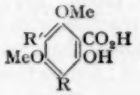
761. *Griseofulvin. Part III.* The Structures of the Oxidation Products* $C_9H_9O_5Cl$ *and* $C_{14}H_{15}O_7Cl$.

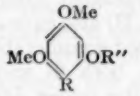
By John Frederick Grove, J. MacMillan, T. P. C. Mulholland, and (Mrs.) J. Zealley.

The oxidation products $C_9H_9O_5Cl$ and $C_{14}H_{15}O_7Cl$ are shown to be 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic (I; R = Cl, R′ = H) and 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid (IV) respectively, as originally suggested by Oxford, Raistrick, and Simonart (*Biochem. J.*, 1939, **33**, 240).

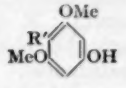
The monobasic acid $C_9H_9O_5Cl$, m. p. 222° (decomp.), obtained as one product in the potassium permanganate oxidation of griseofulvin was shown by Oxford, Raistrick, and Simonart (*Biochem. J.*, 1939, **33**, 240) to give a purple ferric chloride colour typical of a salicylic acid, and to be derived from 2-hydroxy-4 : 6-dimethoxybenzoic acid. 3-Chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (I; R = Cl, R′ = H) was preferred to the 5-chloro-structure (I; R = H, R′ = Cl) on the basis of the negative Millon reaction which was taken to indicate the presence of an *oo*′-disubstituted phenol (Vaubel, *Z. angew. Chem.*, 1900, **13**, 1127). In view of the unreliability of the Millon test when applied to derivatives of sali-



(I)



(II)



(III)

cylic acid, a formal proof of the orientation of the substituents in the griseofulvin oxidation product was essential. This has been achieved by decarboxylation of the acid $C_9H_9O_5Cl$ to a chlorophenol whose structure has been established as 2-chloro-3 : 5-dimethoxyphenol (II; R = Cl, R″ = H) by two unambiguous syntheses.

In the first synthesis, nitration of 3 : 5-dimethoxyphenol gave the steam-volatile 2-nitro-compound (II; R = NO_2, R″ = H) from which the corresponding amine was readily obtained by reduction, its structure as a 2-aminophenol being confirmed by the formation of a 2-methylbenzoxazole.

Attempts to convert the 2-aminophenol directly into the 2-chlorophenol by the Sandmeyer reaction were unsuccessful. Reduction of 3 : 5-dimethoxy-2-nitrophenyl acetate (II; R = NO_2, R″ = Ac) gave only 2-acetamido-3 : 5-dimethoxyphenol (II; R = NHAc, R″ = H) but reduction of the benzyl ether of 3 : 5-dimethoxy-2-nitrophenol gave

* Part II, preceding paper.

the amine (II; R = NH_2, R″ = CH_2Ph). By the Sandmeyer reaction the latter yielded the benzyl ether of 2-chloro-3 : 5-dimethoxyphenol, identical with the benzyl ether of the chlorophenol obtained from the griseofulvin oxidation product, $C_9H_9O_5Cl$.

In the second synthesis, methyl 4-hydroxy-2 : 6-dimethoxybenzoate (III; R′ = CO_2Me) (Pfeffer and Fischer, *Annalen*, 1912, **389**, 207) with sulphuryl chloride in chloroform afforded methyl 3-chloro-4-hydroxy-2 : 6-dimethoxybenzoate. Hydrolysis and decarboxylation were effected in one stage by treatment with concentrated sulphuric acid; the resultant 2-chloro-3 : 5-dimethoxyphenol (II; R = Cl, R″ = H) was identical with the chlorophenol obtained by decarboxylation of the acid $C_9H_9O_5Cl$.

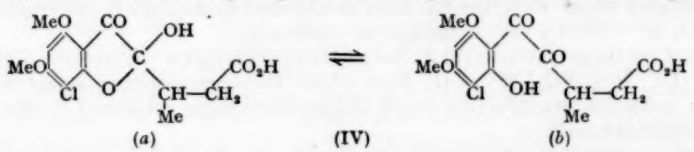
Moreover, methyl 3-chloro-4-hydroxy-2 : 6-dimethoxybenzoate is distinct from the methyl ester of the griseofulvin oxidation product $C_9H_9O_5Cl$.

Attempts to monochlorinate 4-hydroxy-2 : 6-dimethoxybenzoic acid yielded only the 3 : 5-dichloro-derivative, which gave 2 : 6-dichloro-3 : 5-dimethoxyphenol on decarboxylation. All attempts to prepare 4-chloro-3 : 5-dimethoxyphenol (III; R′ = Cl) from the corresponding 4-amino-compound failed. The amine was obtained, (*a*) by catalytic reduction of the 4-nitrophenol which in turn was isolated *inter alia* from the benzene-soluble portion of the non-steam-volatile product from the nitration of 3 : 5-dimethoxyphenol, and (*b*) by reduction of 3 : 5-dimethoxy-4-nitrosophenol prepared by the nitrosation of 3 : 5-dimethoxyphenol (cf. Weidel and Pollak, *Monatsh.*, 1900, **21**, 15).

The unambiguous syntheses of 2-chloro-3 : 5-dimethoxyphenol demonstrate conclusively that the acid $C_9H_9O_5Cl$ is 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (I; R = Cl, R′ = H) as suggested by Oxford *et al.*; but the colour reactions frequently used in orientating phenols can often be misleading. This is borne out by our experience with the two series of compounds obtained by chlorination of 2-hydroxy-4 : 6-dimethoxybenzoic acid and 3 : 5-dimethoxyphenol respectively. Chlorination of 2-hydroxy-4 : 6-dimethoxybenzoic acid (or its silver salt) in carbon tetrachloride solution afforded 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid, identical with the griseofulvin oxidation product, and the isomeric 5-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (I; R = H, R′ = Cl) together with small amounts of 3 : 5-dichloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (I; R = R′ = Cl).

Treatment of 3 : 5-dimethoxyphenol in chloroform with sulphuryl chloride gave the steam-volatile 2- and the non-volatile 4-chloro-3 : 5-dimethoxyphenol (III; R′ = Cl). The 4-chlorophenol was also obtained by decarboxylation of 5-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid.

3 : 5-Dichloro-2-hydroxy-4 : 6-dimethoxybenzoic acid gave a negative Millon reaction but the 5-chloro-compound (I; R = H, R′ = Cl) gave the yellow colour normally obtained with salicylic acids with a free *o*-position. Both acids rapidly gave a strong blue colour with the 2 : 6-dibromoquinone-chloroimide reagent (Gibbs, *J. Biol. Chem.*, 1927, **72**, 649); the 3-chloro-compound (I; R = Cl, R′ = H) also gave a positive reaction with the reagent but rather surprisingly the colour developed considerably more slowly than was the case with the first two substances. Similarly, both 2- and 4-chloro-3 : 5-dimethoxyphenol gave positive reactions with the reagent, the colour developing more rapidly with the latter compound. There is an increasing body of evidence (Davidson, Keane, and Nolan, *Sci. Proc. R. Dublin Soc.*, 1943, **23**, 143; Calam, Clutterbuck, Oxford, and Raistrick, *Biochem. J.*, 1947, **41**, 458) that the Gibbs reagent gives misleading information when the *para*-position



(*a*) (IV) (*b*)

to a hydroxyl group is blocked by a chlorine substituent, and the above results strongly emphasise this conclusion.

Oxford *et al.* (*loc. cit.*), considered the monobasic acid $C_{14}H_{15}O_7Cl$, the second product of the permanganate oxidation of griseofulvin, to be 7-chloro-2-hydroxy-4 : 6-dimethoxy-

coumaran-3-one-2-β-butyric acid (IV*a*), although little evidence was presented in support of this and the mechanism of its formation from griseofulvin was left obscure. The ready formation of the neutral lactone A, $C_{14}H_{13}O_6Cl$, m. p. 220° (Part II), suggested the presence of a γ-hydroxy-carboxylic acid grouping; in addition Oxford *et al.* showed that the acid contained two methoxyl groups and considered that the slow formation of a precipitate with Brady's reagent indicated the presence of a carbonyl group. The presence of these functional groupings has been confirmed. Additional evidence for the carboxyl group comes from the positive hydroxamic acid reaction and from the formation of a methyl ester. Warming with excess of alkali, followed by back-titration, failed to disclose the presence of a second acidic grouping. Although all attempts to prepare a carbonyl derivative failed, the presence of a keto-group is demonstrated by the infra-red spectrum of the methyl ester (Fig. 1) which clearly shows bands at 1735 cm.$^{-1}$ arising from the saturated ester (Grove and Willis, *J.*, 1951, 877) and at 1705 cm.$^{-1}$ attributed to the coumaranone ring. The infra-red spectrum of the acid $C_{14}H_{15}O_7Cl$ (Fig. 1) shows only one intense band (at 1710 cm.$^{-1}$) in the 6-μ region, the characteristic >C=O frequencies of the carboxylic acid residue and the coumaranone ring overlapping. A doublet with maxima at 2640 and 2540 cm.$^{-1}$ in the spectrum of this acid is attributed to –OH stretching vibrations in the carboxyl group.

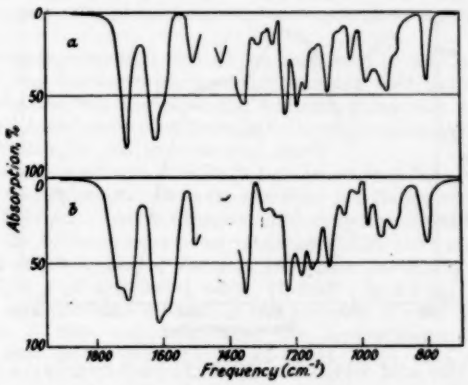


FIG. 1.

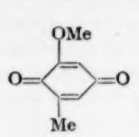
a, *7-Chloro-2-hydroxy-4:6-dimethoxy-coumaran-3-one-2-β-butyric acid.*

b, *Methyl 7-chloro-2-hydroxy-4:6-dimethoxycoumaran-3-one-2-β-butyrate.*

Both the acid and its methyl ester show alcoholic hydroxyl absorption in the region of 3350 cm.$^{-1}$ (acid, 3333; ester, 3356 cm.$^{-1}$). Six of the seven oxygen atoms in this acid are contained in the carboxyl, two methoxyl, carbonyl, and hydroxyl groupings, leaving one unaccounted for, presumably in an ether linkage. Microhydrogenation showed the absence of ethylenic bonds. The ultra-violet absorption curve (Fig. 2) retains the main chromophoric system of griseofulvin and is characteristic of a compound in which phloroglucinol and carbonyl chromophores are conjugated. The acid $C_{14}H_{15}O_7Cl$ therefore contains an aromatic ring and it follows from what is known about the oxygen function that it must contain one further ring. A Kühn–Roth oxidation shows the presence of one *C*-methyl group. All the evidence set out above can be quoted in support of structure (IV*a*). Final proof of this structure (or of a similar one in which the methyl group is attached to the α- instead of to the β-carbon atom) comes from the oxidation with periodic acid, in which 1 mol. of periodate is consumed and the acid $C_{14}H_{15}O_7Cl$ is split quantitatively into 3-chloro-2-hydroxy-4:6-dimethoxybenzoic acid and (+)-methylsuccinic acid, identical with an authentic specimen.* (+)-Methylsuccinic acid is also isolated when the acid $C_{14}H_{15}O_7Cl$ is

* Comparison of the infra-red spectra of the natural and the synthetic (+)-methylsuccinic acids was carried out by Mr. T. A. Kletz, Imperial Chemical Industries Limited, Billingham Division, using a reflecting microscope attached to an infra-red spectrometer. A considerable difference existed between the spectrum of a sublimed sample of (+)-methylsuccinic acid and that of a specimen crystallised from a solvent. Similar differences existed in the spectra of specimens of (±)-methylsuccinic acid prepared by sublimation and crystallisation, and these also differed slightly from the corresponding spectra of the optically active material. This matter has been further investigated in these laboratories by Dr. L. A. Duncanson and is the subject of a separate communication (*J.*, 1952, 1753).

oxidised with chromic acid; the formation of 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid when the compound is oxidised with permanganate in acetone has already been reported (Part II).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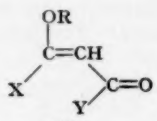
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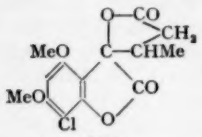
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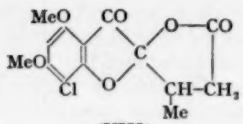
(VIII)

3-Methoxy-2 : 5-toluquinone (V), obtained by chromic oxide oxidation of griseofulvin (Part II), contains the enolic ether system (VI) which is believed to be present in griseofulvin (Part I) and is attacked in the permanganate oxidation. It follows that the keto-group at position 2 in 3-methoxy-2 : 5-toluquinone must arise by the rupture of a bond or bonds attaching the carbon atom at this position to the rest of the griseofulvin molecule and that the carbonyl group at position 5 in the quinone corresponds to the carboxyl group in the acid $C_{14}H_{15}O_7Cl$. The methyl group must therefore be in the β-position to the carboxyl group

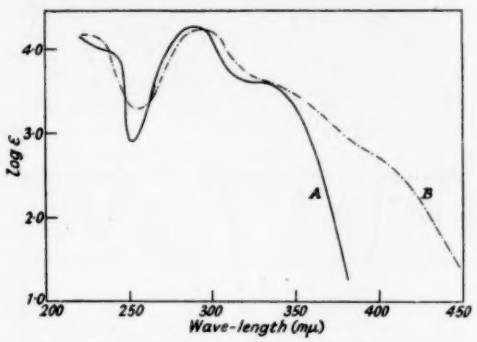

FIG. 2. *Ultra-violet absorption of 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid :*

A, in methanol;
B, in 0·1N-sodium hydroxide.

in this acid which has the 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid structure (IV*a*) proposed by Oxford *et al.*

Structure (IV) should be capable of showing tautomerism and although the compound exists in the cyclic semiacetal form (IV*a*) (cf. Erdtman, *Research*, 1950, **3**, 63) in the solid state (as shown by the alcoholic hydroxyl absorption in the infra-red spectrum) and in methanol solution (as shown by the ultra-violet absorption spectrum), the presence of the open chain form (IV*b*) is demonstrated by the absorption curve in alkaline solution (Fig. 2, band near 420 mμ characteristic of –CO·CO–). 7-Chloro-2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid is stable to acid hydrolysis but in boiling 3N-sodium hydroxide undergoes benzilic acid rearrangement to a dilactone (VII) isomeric with lactones A and B (VIII) (Part II).

EXPERIMENTAL

M. p.s are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford, and by Mr. W. Brown.

Nitration of 3 : 5-*Dimethoxyphenol.*—To a well-stirred solution of 3 : 5-dimethoxyphenol (25 g.) in acetic acid (100 ml.) and acetic anhydride (60 ml.) at −5° to 0°, there was added dropwise (½ hour) nitric acid (*d*, 1·42; 16 g.) in acetic acid (50 ml.). After 2 hours at room temperature the mixture was poured over cracked ice (500 g.). The combined crude product from two experiments was steam-distilled. The first litre of distillate, deep orange and containing most of the acetic acid, was discarded and distillation continued until no more solid crystallised from the distillate (60 l.). The 3 : 5-dimethoxy-2-nitrophenol (13·0 g., 20%) which separated at 0° was collected and recrystallised from ethanol in yellow needles or plates, m. p. 130° (Found: C, 48·2, 48·3; H, 4·7, 4·5; N, 7·2, 7·2. $C_8H_9O_5N$ requires C, 48·2; H, 4·6; N, 7·0%). 3 : 5-Dimethoxy-2-nitrophenol formed an orange solution in aqueous sodium hydroxide and gave a

brownish colour with ferric chloride in ethanol. The *acetate* formed pale yellow prisms, m. p. 123°, from ethanol (Found: C, 50·1; H, 4·7; N, 5·9. $C_{10}H_{11}O_6N$ requires C, 49·8; H, 4·6; N, 5·8%). The O-*benzyl ether* formed pale yellow needles, m. p. 100°, from ethanol (Found: C, 62·5; H, 5·3; N, 4·75. $C_{15}H_{15}O_5N$ requires C, 62·3; H, 5·2; N, 4·8%).

The pitch-like residue from the steam-distillation was separated from the residual aqueous liquor by decantation, dried by the repeated addition and evaporation of benzene, and then extracted for 6 hours with benzene in a Soxhlet apparatus. The benzene-insoluble material (30 g.) was discarded. The dried benzene-soluble extract was concentrated to 300 ml. and chromatographed on alumina (pH 4; grade II). The following bands (from bottom to top) were obtained and eluted with benzene: (i) A yellow band which passed rapidly down the column and furnished on recovery yellow needles (0·30 g.), m. p. 256° (decomp.), of 2 : 6-dimethoxy-*p*-benzoquinone (Found: C, 57·5; H, 5·1. Calc. for $C_8H_8O_4$: C, 57·1; H, 4·8%). (ii) A band, colourless in daylight but showing a pale blue fluorescence in ultra-violet light, which yielded only gum (20 mg.). (iii) A yellow band giving, on recovery, 3·5 g. of a yellow solid, m. p. 125—170°, which was separated by fractional crystallisation from benzene into 3 : 5-dimethoxy-2-nitrophenol, m. p. 128—130° (1·05 g.), and 3 : 5-*dimethoxy-4-nitrophenol* (1·2 g., 2%), lemon yellow needles (from benzene), m. p. 168° (Found: C, 48·2; H, 4·7; N, 6·8. $C_8H_9O_6N$ requires C, 48·2; H, 4·6; N, 7·0%) [*acetate*, almost colourless prisms (from ethanol), m. p. 101° (Found: C, 50·1; H, 4·7; N, 5·8. $C_{10}H_{11}O_6N$ requires C, 49·8; H, 4·6; N, 5·8%)]. The remaining bands were eluted with benzene + 1% of methanol and the substances isolated from them will be reported later.

3 : 5-*Dimethoxy-4-nitrosophenol*.—3 : 5-Dimethoxyphenol (2·0 g.), in methanol (2 ml.) and concentrated hydrochloric acid (2 ml.), at 0°, was treated in portions, with shaking, with sodium nitrite (1·0 g.) in water (4 ml.). When addition was complete the 4-nitroso-compound was collected, washed with water, and crystallised from acetic acid, forming brick-red needles (1·0—1·6 g.), decomp. above 220°. (Weidel and Pollak, *loc. cit.*, give decomp. 222°.)

2-*Amino*-3 : 5-*dimethoxyphenol*.—3 : 5-Dimethoxy-2-nitrophenol (3·5 g.) in ethanol (200 ml.) was reduced by shaking it with hydrogen at room temperature in the presence of a Raney nickel catalyst (0·5 g.) (absorption: 3 mols. in 2 hours). After filtration and evaporation of the solvent under reduced pressure in nitrogen, the brown product was sublimed at 120°/10^{-3} mm., yielding colourless crystalline 2-*amino*-3 : 5-*dimethoxyphenol*, decomp. 150° after darkening at 142° (Found: C, 57·1; H, 6·6; N, 8·3. $C_8H_{11}O_3N$ requires C, 56·8; H, 6·55; N, 8·3%). It slowly darkened, and was rapidly oxidised in solution in ethanol in the presence of air. The hydrochloride formed colourless needles, m. p. 205° (decomp.), from 15% hydrochloric acid (Weidel and Pollak, *loc. cit.*, give m. p. 205—206°) (Found: C, 42·8; H, 6·3. Calc. for $C_8H_{11}O_3N,HCl,H_2O$: C, 42·95; H, 6·3%).

The neutral ON-*diacetyl* derivative, obtained by heating 2-amino-3 : 5-dimethoxyphenol (0·2 g.) under reflux with acetic anhydride (2 ml.) for 1 hour, formed colourless prisms (0·18 g.), m. p. 93°, from ethanol (Found: C, 57·2; H, 5·9; N, 4·8, 5·1; OMe, 21·2; Ac, 32·2%; *M*, 226. $C_{12}H_{15}O_5N$ requires C, 56·9; H, 6·0; N, 5·5; 2OMe, 24·5; 2Ac, 34·0%; *M*, 253). (The triacetyl compound $C_{14}H_{17}O_6N$ requires C, 56·9; H, 5·8; N, 4·75; 3Ac, 43·7%; *M*, 295.) The diacetyl derivative was insoluble in both dilute hydrochloric acid and in sodium hydroxide.

4 : 6-*Dimethoxy-2-methylbenzoxazole*.—2-Amino-3 : 5-dimethoxyphenol (0·18 g.) and acetic anhydride (2 ml.) were heated under reflux for 24 hours, excess of acetic acid removed, and the residual oil heated at 220° for several minutes (distillation of volatile material and darkening of residue). The ethereal solution of the residue was extracted with 3N-hydrochloric acid, and the extract basified, affording a brown oil which crystallised from light petroleum (b. p. 60—80°) in colourless needles (43 mg.), m. p. 78°, of 4 : 6-*dimethoxy-2-methylbenzoxazole* (Found: C, 62·4; H, 5·8; N, 7·5. $C_{10}H_{11}O_3N$ requires C, 62·1; H, 5·7; N, 7·3%). The neutral ethereal fraction gave on recovery the above diacetyl compound, m. p. 93° (10 mg.).

4-*Amino*-3 : 5-*dimethoxyphenol*.—(*a*) 3 : 5-Dimethoxy-4-nitrophenol (0·7 g.) in ethanol (40 ml.) absorbed 3 mols. of hydrogen at room temperature in the presence of a Raney nickel catalyst (18 hours). After removal of the catalyst and evaporation under reduced pressure in nitrogen the product was sublimed at 130°/10^{-3} mm., giving a colourless sublimate (0·45 g.) of 4-*amino*-3 : 5-*dimethoxyphenol*, which crystallised from ethyl acetate in needles, m. p. in a sealed tube 165—180° (decomp.) (Found: C, 56·9; H, 6·7. $C_8H_{11}O_3N$ requires C, 56·8; H, 6·55%). The hydrochloride, decomp. from 200°, was obtained in colourless needles from 15% hydrochloric acid (Weidel and Pollak, *loc. cit.*, give m. p. 171—173°) (Found: C, 43·0; H, 6·1; Cl, 15·8. Calc. for $C_8H_{11}O_3N,HCl,H_2O$: C, 42·95; H, 6·3; Cl, 15·8%).

The ON-*diacetyl* derivative, insoluble in both dilute sodium hydroxide solution and dilute

hydrochloric acid, formed colourless plates, m. p. 169°, from ethanol (Found: C, 56·9; H, 5·9; N, 5·0, 5·0; Ac, 36·5. $C_{12}H_{15}O_5N$ requires C, 56·9; H, 6·0; N, 5·5; 2Ac, 34·0%).

(*b*) 3 : 5-Dimethoxy-4-nitrosophenol (1·0 g.) in 30% aqueous ammonia (10 ml.) was filtered from insoluble material and saturated with hydrogen sulphide until the dark red colour was discharged (½ hour) and thereafter for ½ hour. The colourless needles of the 4-aminophenol were collected (800 mg.), decomposing above 170°. The diacetyl derivative formed colourless needles (from methanol), m. p. 167°, not depressed by the material obtained as in (*a*) above.

Reduction of 3 : 5-*Dimethoxy-2-nitrophenyl Acetate.*—(a) *With Raney nickel.* The acetate (5·5 g.) in ethanol (500 ml.) was hydrogenated as described above for the reduction of 3 : 5-dimethoxy-2-nitrophenol. Removal of the solvent left a greenish-brown solid (3·0 g.), m. p. 110—112°, immediately soluble in 3N-sodium hydroxide and only slowly dissolving in 3N-hydrochloric acid; on sublimation at 150°/10^{-3} mm. followed by crystallisation from ether, it gave colourless prisms of 2-*acetamido*-3 : 5-*dimethoxyphenol*, m. p. 112—114° (Found: C, 57·1; H, 6·4; N, 7·0. $C_{10}H_{13}O_4N$ requires C, 56·8; H, 6·2; N, 6·6%). It gave a green colour with ferric chloride. Acetylation under reflux with acetic anhydride yielded the diacetate, m. p. 93°, identical with the diacetate obtained above from 2-amino-3 : 5-dimethoxyphenol.

(b) *With Adams's catalyst.* The acetate (0·8 g.) in ethanol (55 ml.) in the presence of Adams's platinum oxide catalyst (0·08 g.) slowly absorbed 120 ml. of hydrogen during 10 hours and reduction then ceased (Calc.: $3H_2$, 250 ml.). After evaporation under reduced pressure in nitrogen, the dark solid residue was taken up in ether and extracted with 3N-hydrochloric acid.

The ethereal layer yielded, on recovery and crystallisation from ethanol, unchanged starting material, m. p. 123° (0·20 g.). The acid washings were cooled to 0°, neutralised with ice-cold 3N-sodium hydroxide and extracted with ether. , The dark brown solid obtained on recovery was now insoluble in 3N-hydrochloric acid and crystallised from light petroleum (b. p. 60—80°) (charcoal) in prisms, m. p. 108—111° (60 mg.), not depressed by admixture with 2-acetamido-3 : 5-dimethoxyphenol.

Attempted Sandmeyer Reactions.—(a) *With* 2-*amino*-3 : 5-*dimethoxyphenol.* The diazonium hydrochloride and sulphate were obtained in solution in the usual way but attempts, using a wide variety of experimental conditions, to obtain 2-chloro-3 : 5-dimethoxyphenol by the action of cuprous chloride were unsuccessful.

(b) *With* 4-*amino*-3 : 5-*dimethoxyphenol.* Diazotisation followed by treatment with cuprous chloride gave only 2 : 6-dimethoxy-*p*-benzoquinone as yellow needles, m. p. 256° (decomp.) (Found: C, 57·1; H, 5·1; OMe, 37·2. Calc. for $C_8H_8O_4$: C, 57·1; H, 4·8; 2OMe, 36·9%). This gave an intense purple colour with concentrated sulphuric acid. Diazotisation in the presence of stannous chloride (cf. Kozlov, *J. Gen. Chem., U.S.S.R.*, 1937, **7**, 1635), but not cupric sulphate, largely prevented the formation of the quinone but no 4-chloro-3 : 5-dimethoxyphenol was obtained on treatment of the diazo-solutions with cuprous chloride.

Reduction of the Benzyl Ether (II; R = NO_2, R″ = CH_2Ph).—To a boiling solution of the benzyl ether (3·00 g.) in ethanol (100 ml.) and water (120 ml.) was added in portions during 10 minutes, sodium hydrosulphite (dithionite) (15 g.) until the liquid was almost colourless. After removal of most of the ethanol under reduced pressure, the residual oily emulsion was rendered alkaline by the addition of 3N-sodium hydroxide (25 ml.) and extracted with ether. The ethereal extract was washed with 3N-sodium hydroxide and water and on recovery gave a pale brown oil which did not crystallise. On the addition of concentrated hydrochloric acid to the oil, the *hydrochloride* of the amine (II; R = NH_2, R″ = CH_2Ph) separated and was collected, washed with 3N-hydrochloric acid, and dried over solid sodium hydroxide (2·32 g., 76%). The hydrochloride tended to colour in air; after two crystallisations from 3N-hydrochloric acid (charcoal) it formed long colourless needles, m. p. 200—202° (decomp.) (rapid heating) (Found: C, 61·0; H, 5·6; Cl, 13·2; N, 5·5. $C_{15}H_{18}O_3NCl$ requires C, 60·9; H, 6·1; Cl, 12·0; N, 4·7%). The oily amine obtained on basification of the hydrochloride was insoluble in sodium hydroxide and gave a purple colour with ferric chloride solution. The *acetyl* derivative, formed when the free amine (100 mg.) was heated with acetic anhydride (0·5 ml.) and acetic acid (0·5 ml.) at 100° for 30 seconds, crystallised from aqueous ethanol in colourless plates (110 mg.), m. p. 146—147° (Found: C, 67·5, 67·8; H, 6·4, 6·3; $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·4%). The NN-*diacetyl* derivative was obtained when the free amine (0·2 g.) was heated under reflux with acetic anhydride (1 ml.) for 5 minutes. It formed colourless plates (231 mg.) (from aqueous ethanol), m. p. 111—112° (Found: C, 66·5; H, 6·2; N, 4·0. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·2; N, 4·1%).

Sandmeyer Reaction of the Amine (II; R = NH_2, R″ = CH_2Ph).—The amine hydrochloride (590 mg., 2 millimols.) in N-hydrochloric acid (6 ml.) was diazotised in the usual way by the

addition of sodium nitrite (152 mg., 2·2 millimols.) in water (0·6 ml.). After filtration from a little dark amorphous material, the clear solution was added to a vigorously stirred solution of cuprous chloride in concentrated hydrochloric acid (3 ml., 3 millimols.) at 0° and the mixture allowed to warm to room temperature. Ether was then added and stirring continued for 15 minutes, after which the ether was replaced by benzene and the temperature raised to 80°. Stirring was continued for 1 hour, the benzene being replaced at intervals of 15 minutes. The combined organic extracts (40 ml.) were washed with water and, after removal of the solvent, the residue was taken up in ether and washed with 3N-sodium hydroxide and water. The dark oil obtained on recovery was distilled at 130°/10^{-3} mm.; the pale yellow distillate (42 mg.) crystallised from ether in colourless prisms of *benzyl 2-chloro-3 : 5-dimethoxyphenyl ether*, m. p. 71—72° (21 mg.), identical by mixed m. p. and infra-red absorption spectrum with the benzyl ether of the chlorophenol obtained by decarboxylation of the griseofulvin oxidation product, $C_9H_9O_5Cl$ (see below) (Found: C, 64·6; H, 5·4; Cl, 12·6. $C_{15}H_{15}O_3Cl$ requires C, 64·6; H, 5·4; 12·7%).

Decarboxylation of the Griseofulvin Oxidation Product $C_9H_9O_5Cl$ (*3-Chloro-2-hydroxy-4 : 6-dimethoxybenzoic Acid*).—The acid (0·1 g.) was heated in redistilled quinoline (5 ml.) with copper chromite (0·1 g.), whilst a stream of carbon dioxide-free nitrogen was passed through the apparatus. Evolution of carbon dioxide was complete in 45 minutes at a bath temperature of 160° (total CO_2 evolved = 1·04 mols.). After removal of the catalyst, the filtrate was poured into 3N-hydrochloric acid (25 ml.) and extracted continuously with ether for some hours. The ethereal extract was washed with 3N-hydrochloric acid, concentrated to 20 ml., and extracted first with saturated sodium carbonate solution and then with 3N-sodium hydroxide. The sodium hydroxide extract was acidified with concentrated hydrochloric acid and re-extracted with ether. Evaporation left a tar which partly solidified and then sublimed at 70°/10^{-2} mm. The colourless sublimate (30 mg.; m. p. 54°) crystallised from light petroleum (b. p. 60—80°) in needles of *2-chloro-3 : 5-dimethoxyphenol*, m. p. 60°, identical with a synthetic specimen (Found: C, 51·2; H, 5·1; Cl, 18·9. $C_8H_9O_3Cl$ requires C, 50·9; H, 4·8; Cl, 18·8%). The carbonate extract on acidification and working up in a similar manner yielded a further 20 mg. of the same phenol, m. p. 58°. 2-Chloro-3 : 5-dimethoxyphenol gave a blue colour with ferric chloride and positive Millon's and Gibbs's reactions.

The benzyl ether (II; R = Cl, R″ = CH_2Ph) was prepared by treatment of the phenol (1·88 g.) with benzyl bromide (1·75 g.) and anhydrous potassium carbonate (2·3 g.) in boiling acetone (20 ml.) for 2½ hours, and the crude product (2·5 g.) after two crystallisations from ether was obtained in colourless prisms, m. p. 71—72°, identical with the material obtained from the Sandmeyer reaction on the amine (II; R = NH_2, R″ = CH_2Ph).

Decarboxylation of 5-Chloro-2-hydroxy-4 : 6-dimethoxybenzoic Acid.—The acid (179 mg.) was decarboxylated by the method described above, 0·83 mol. of carbon dioxide being evolved in 1 hour at 180°. The ethereal extract was extracted with 3N-sodium hydroxide and after acidification, recovery, and sublimation the colourless sublimate (35 mg., m. p. 115—140°) was fractionally crystallised from benzene, giving unchanged starting material, needles (5 mg.), m. p. 138—140°, and 4-chloro-3 : 5-dimethoxyphenol, prisms (10 mg.), m. p. 130—132°, not depressed by mixture with the specimen obtained by the direct chlorination of 3 : 5-dimethoxyphenol.

Methyl Ester of the Griseofulvin Oxidation Product $C_9H_9O_5Cl$ (*Methyl 3-Chloro-2-hydroxy-4 : 6-dimethoxybenzoate*).—The acid $C_9H_9O_5Cl$ (70 mg.), suspended in ether (50 ml.), was treated with diazomethane (from 5 g. of nitrosomethylurea) in ether (50 ml.) and kept overnight. The solid was collected, combined with the solid obtained by concentration of the ethereal mother-liquors, and successively extracted with saturated sodium hydrogen carbonate solution and 3N-sodium hydroxide. Acidification of the former yielded a trace of the acid $C_9H_9O_5Cl$, identified by a mixed m. p. determination. The sodium hydroxide extract on acidification yielded *methyl 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoate*, colourless needles (40 mg.) (from ethyl methyl ketone), m. p. 186—187° (Found: C, 48·5; H, 4·3; Cl, 14·05. $C_{10}H_{11}O_5Cl$ requires C, 48·8; H, 4·5; Cl, 14·4%). The neutral material crystallised from light petroleum (b. p. 60—80°) in colourless needles (15 mg.), m. p. 126—127° undepressed on admixture with methyl 3-chloro-2 : 4 : 6-trimethoxybenzoate (Calam and Oxford, *J.*, 1939, 280).

Methyl 4-hydroxy-2 : 6-dimethoxybenzoate, prepared from 2 : 4 : 6-trihydroxybenzoic acid in 60% overall yield by the method of Pfeffer and Fischer (*loc. cit.*), formed colourless needles (from aqueous methanol), m. p. 184—186° (Found: C, 56·8; H, 5·8; OMe, 41·0. Calc. for $C_{10}H_{12}O_5$: C, 56·6; H, 5·7; 3OMe, 43·9%).

Methyl 3-Chloro-4-hydroxy-2 : 6-dimethoxybenzoate.—The above ester (200 mg.) in dry chloroform (35 ml.) was treated with sulphuryl chloride (135 mg.) in chloroform (1 ml.) and set aside

overnight. After being washed with water, the dried chloroform solution was concentrated, yielding the 3-*chloro*-compound (200 mg.), m. p. 153—154°, colourless needles from benzene (Found: C, 49·0; H, 4·5; Cl, 14·1. $C_{10}H_{11}O_5Cl$ requires C, 48·8; H, 4·5; Cl, 14·4%). This chloro-ester was distinct (mixed m. p. and infra-red spectrum) from the methyl ester of the griseofulvin oxidation product $C_9H_9O_5Cl$ described above.

2-*Chloro*-3 : 5-*dimethoxyphenol*.—The above chloro-compound (100 mg.) was dissolved in ice-cold sulphuric acid (0·1 ml.) and the solution, after being kept at 30° for 2 hours, was poured on crushed ice (500 mg.). The diluted reaction mixture was then heated at 100° for several minutes, cooled, and extracted with ether. The recovered gum was sublimed at 75°/0·1 mm., affording 2-chloro-3 : 5-dimethoxyphenol which crystallised from light petroleum (b. p. 40—60°) in colourless needles (60 mg.), m. p. 60—61° undepressed on admixture with the phenol, m. p. 60°, obtained from griseofulvin.

3 : 5-*Dichloro*-4-*hydroxy*-2 : 6-*dimethoxybenzoic Acid*.—(*a*) 4-Hydroxy-2 : 6-dimethoxybenzoic acid (396 mg.), m. p. 177° (decomp.), prepared by hydrolysis of the corresponding ester described above, was suspended in dry carbon tetrachloride (20 ml.) and treated with chlorine (150 mg.) in carbon tetrachloride (5 ml.). After 3 hours, the solid was collected, extracted with hot carbon tetrachloride (15 ml.), and filtered from unchanged starting material (180 mg.). On cooling, the carbon tetrachloride extract furnished the 3 : 5-*dichloro*-derivative as colourless needles (110 mg.) m. p. 125° (Found: C, 41·1; H, 3·3; Cl, 25·8. $C_9H_8O_5Cl_2$ requires C, 40·45; H, 3·0; Cl, 26·6%).

(*b*) 4-Hydroxy-2 : 6-dimethoxybenzoic acid (180 mg.), suspended in carbon tetrachloride (30 ml.), was heated under reflux with chlorine (250 mg.) in carbon tetrachloride (15 ml.) until complete solution was effected. By next morning the solution had deposited the 3 : 5-dichloro-compound in colourless needles (150 mg.), m. p. 125°.

2 : 6-*Dichloro*-3 : 5-*dimethoxyphenol*.—(*a*) 3 : 5-Dichloro-4-hydroxy-2 : 6-dimethoxybenzoic acid (100 mg.) in quinoline (2 ml.) was heated at 125—130° with copper chromite (40 mg.) in a stream of nitrogen. The evolution of carbon dioxide was complete in 1 hour. The cooled quinoline solution was poured into 3N-hydrochloric acid and extracted with ether. Recovery of the ethereal extract gave 2 : 6-*dichloro*-3 : 5-*dimethoxyphenol* (60 mg.), colourless needles [from benzene–light petroleum (b. p. 60—80°)], m. p. 147—149° (Found: C, 43·3; H, 3·9; Cl, 31·4. $C_8H_8O_3Cl_2$ requires C, 43·05; H, 3·6; Cl, 31·8%).

(*b*) 3 : 5-Dichloro-4-hydroxy-2 : 6-dimethoxybenzoic acid (100 mg.) in 2N-hydrochloric acid (2 ml.) was heated under reflux in a stream of nitrogen. Evolution of carbon dioxide was complete in 1 hour. The dichlorophenol which had begun to crystallise from the reaction was collected after ½ hour and crystallised as above, forming colourless needles (60 mg.), m. p. 147—149°.

Chlorination of 3 : 5-*Dimethoxyphenol*.—3 : 5-Dimethoxyphenol (2·0 g.), in dry chloroform (15 ml.) was vigorously shaken while sulphuryl chloride (1·75 g.) in chloroform (10 ml.) was added dropwise. After 48 hours, the chloroform was removed by distillation and the residual brown gum was distilled in steam (500 ml. of distillate). The volatile colourless oil, recovered by ether-extraction, crystallised from light petroleum in long needles (300 mg.), m. p. 58—59°, undepressed on admixture with 2-chloro-3 : 5-dimethoxyphenol prepared above.

Crystallisation of the non-steam volatile fraction from benzene afforded 4-*chloro*-3 : 5-*dimethoxyphenol* as small colourless needles (240 mg.), m. p. 132—133° (Found: C, 51·0; H, 4·85; Cl, 18·95. $C_8H_9O_3Cl$ requires C, 50·9; H, 4·8; Cl, 18·8%). The *benzyl ether* crystallised from ether in colourless plates, m. p. 97—98° (Found: C, 64·6; H, 5·5; Cl, 12·4. $C_{15}H_{15}O_3Cl$ requires C, 64·6; H, 5·4; Cl, 12·7%). The 4-chloro-phenol readily sublimed at 110—120° (oil-bath) and 0·1 mm. Hg and gave a positive reaction with the Gibbs reagent, the blue colour developing much more rapidly than with the above 2-chloro-derivative.

The residue, obtained by recovery of the benzene mother-liquors from crystallisation of the 4-chloro-compound, partly distilled at 110° (oil-bath) and 0·1 mm. Hg, affording a further 650 mg. of the 2-chloro-compound. The residue from the distillation sublimed at 120° (oil-bath)/0·1 mm., giving the 4-chloro-derivative (200 mg.).

Chlorination of 2-*Hydroxy*-4 : 6-*dimethoxybenzoic Acid*.—(*a*) 2-Hydroxy-4 : 6-dimethoxybenzoic acid (2·0 g.) was dissolved in 1% sodium hydroxide solution (40 ml.), excess of silver nitrate (1·8 g.) in water added, and the white precipitate collected, washed with water, and dried to constant weight at 100—106° (2·54 g., 82%). The dried silver salt was suspended in dry carbon tetrachloride (30 ml.), and chlorine in carbon tetrachloride (10 ml., 0·67 g. of chlorine) added dropwise under anhydrous conditions. The mixture was heated cautiously on the water-bath and then under reflux for 3 hours. The hot solution was filtered and the solid material washed with sodium hydrogen sulphite solution (1%) and then with sodium hydrogen

carbonate solution (1%). The white solid, which was precipitated on acidification of the bicarbonate washings, was collected (1·35 g.); it had m. p. 190—220° and recrystallised from ethyl acetate, giving 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid as colourless needles, m. p. 220—223° (decomp.) undepressed on admixture with the acid $C_9H_9O_5Cl$ obtained from griseofulvin (Part II) (Found : C, 46·65; H, 4·2. Calc. for $C_9H_9O_5Cl$: C, 46·5; H, 3·9%).

On cooling, the carbon tetrachloride filtrate deposited unchanged starting material, m. p. and mixed m. p. 150—157° (0·233 g.). Evaporation of the solution gave a yellow solid, m. p. 110—130° (0·42 g.), which was acidic and gave a purple colour in ethanol with ferric chloride. It was taken up in ether (20 ml.) and extracted with saturated sodium hydrogen carbonate solution (3 × 10 ml.). Acidification of this extract gave a white solid, m. p. 125—132°, which resisted further purification by crystallisation. Conversion into the silver salt and recovery followed by two crystallisations from water furnished colourless needles of *5-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid*, m. p. 139—140° (0·2 g.) (Found : C, 46·7; H, 4·0; Cl, 15·05; OMe, 27·0%; equiv., 240. $C_9H_9O_5Cl$ requires C, 46·5; H, 3·9; Cl, 15·2; 2OMe, 26·7%; equiv., 233). This acid gave a positive Gibbs reaction, a yellow colour with Millon's reagent, and a deep purple colour with ferric chloride in ethanol. On methylation in methanol solution with ethereal diazomethane, methyl 3-chloro-2 : 4 : 6-trimethoxybenzoate, m. p. 126°, was obtained, identical with a synthetic specimen.

(*b*) 2-Hydroxy-4 : 6-dimethoxybenzoic acid (2·0 g.) was suspended in carbon tetrachloride (20 ml.), and a solution of chlorine in the same solvent (10·8 ml., 0·72 g. of chlorine) slowly added at room temperature. The mixture was heated under reflux for 3 hours, then filtered hot, and the insoluble material (1·22 g.; m. p. 120—180°) extracted with boiling ethyl acetate (18 ml.). The ethyl acetate-insoluble fraction (0·28 g.) furnished on crystallisation from a larger volume of ethyl acetate colourless needles of 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid, m. p. 220° (decomp.). The ethyl acetate-soluble fraction, after extensive fractional crystallisation first from ethyl acetate and then from benzene, gave a further small fraction of 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (50 mg.), unchanged 2-hydroxy-4 : 6-dimethoxybenzoic acid (26 mg.), a colourless substance, m. p. 175—180° (0·15 g.), and a large fraction (0·46 g.), m. p. 125—140°, which consisted mainly of 5-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid.

The colourless material, m. p. 175—180°, was sublimed at 140°/10^{-4} mm. and then crystallised three times from benzene; it formed long colourless needles of *3 : 5-dichloro-2-hydroxy-4 : 6-dimethoxybenzoic acid*, m. p. 181—182° (Found : C, 40·6; H, 3·2; Cl, 27·4. $C_9H_8O_5Cl_2$ requires C, 40·5; H, 3·0; Cl, 26·6%). 3 : 5-Dichloro-2-hydroxy-4 : 6-dimethoxybenzoic acid gave a deep purple colour with ferric chloride in ethanol and a negative Millon reaction. With the Gibbs reagent a deep blue colour rapidly developed.

On cooling, the carbon tetrachloride mother-liquor from the reaction mixture deposited crystalline material (0·7 g.; m. p. 120—130°) from which 3 : 5-dichloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (27 mg.), 2-hydroxy-4 : 6-dimethoxybenzoic acid (50 mg.), and impure 5-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (0·25 g.; m. p. 125—140°) were obtained after fractional crystallisation from ethyl acetate and benzene.

7-Chloro-2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric Acid (IV), prepared by the oxidation of griseofulvin with zinc permanganate as described in Part II, was fractionally crystallised from ethyl acetate. The first fraction which contained traces of 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid was rejected. Subsequent fractions were combined and recrystallised from ethyl methyl ketone–light petroleum (b. p. 60—80°) in needles, m. p. 190° (decomp.), and were sufficiently pure for degradative work although alkaline hydrolysis (see below) revealed the presence, in some batches only, of traces of 7-chloro-4 : 6-dimethoxycoumaranone-2-β-butyric acid. Further purification raised the m. p. to 204° (decomp.) (Found : C, 51·0; H, 4·7; OMe, 18·0; *C*-Me, 3·7%; equiv., 323. Calc. for $C_{14}H_{15}O_7Cl$: C, 50·8; H, 4·6; 2OMe, 18·8; 1*C*-Me, 4·5%; equiv., 330·5), $[\alpha]_D^{18}$ −12° (*c*, 0·98 in acetone). Ultra-violet absorption max. : 331, 288, ~244 mμ, log ε 3·63, 4·28, 3·95 in methanol; ~405, ~330, 296, ~231 mμ, log ε 2·64, 3·63, 4·26, 4·18 in 0·1N-sodium hydroxide. It gave no colour with ferric chloride. It did not couple with diazotised amines and the Millon and the Gibbs reaction were negative. The hydroxamic acid test for the carboxyl group was positive.

Contrary to the findings of Oxford *et al.*, pure specimens of the acid did not reduce Fehling's solutions or ammoniacal silver nitrate. It did not form derivatives on treatment with Brady's reagent or with phenylhydrazine and was recovered unchanged after attempted reaction with semicarbazide and with hydroxylamine. The acid was recovered unchanged after 1 hour's heating under reflux with 3N-sulphuric acid.

The acid (72·0 mg.) in 0·1032N-sodium hydroxide (5·00 ml.) was heated on the steam-bath

for 1 hour, cooled, and back-titrated with 0·0865N-hydrochloric acid (phenolphthalein). 3·78 ml. of acid were required, whence 1·83 ml. sodium hydroxide were used (Calc. for $1CO_2H$: 2·08 ml.).

The *methyl* ester, obtained by reaction with 10% methanolic hydrochloric acid, sublimed at 120°/10^{-4} mm. in prisms, m. p. 54—58°, not raised by further sublimation (Found : C, 52·3; H, 5·1; Cl, 10·1; OMe, 27·8. $C_{15}H_{17}O_7Cl$ requires C, 52·3; H, 5·0; Cl, 10·3; 3OMe, 27·1%). The methyl ester did not couple with diazotised nitraniline. It was insoluble in water and neutral to the Universal indicator but dissolved slowly in sodium carbonate and more rapidly in sodium hydroxide giving yellow solutions. It did not give a precipitate with Brady's reagent.

Periodate Oxidation of 7-Chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric Acid.—To the acid (311 mg.) in water (60 ml.), 0·092N-sodium periodate (160 ml.) and concentrated hydrochloric acid (2 ml.) were added. After 48 hours at room temperature, the precipitated solid was collected and washed with water, and the combined filtrate and washings were made up to 250 ml. (Titration of a 25 ml. portion of this solution indicated the consumption of 1·05 mols. periodate.) The precipitate (176 mg., 80%) crystallised from ethyl acetate in colourless needles (110 mg.), m. p. and mixed m. p. with 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid, 216—218° (decomp.).

The aqueous filtrate was continuously extracted with ether for 14 hours. The gum, obtained on recovery, sublimed at 100—103°/10^{-3} mm. as a yellow solid which was crystallised from benzene and resublimed (20 mg.). Crystallisation from water gave needles, m. p. 108—110° undepressed on admixture with synthetic (±)- and (+)-methylsuccinic acids and with the product of the chromic oxide oxidation of the acid $C_{14}H_{15}O_7Cl$ (see below). The acid had $[\alpha]_D^{19}$ +9·7° (*c*, 1·48 in water) (Found : C, 45·4; H, 6·1. Calc. for $C_5H_8O_4$: C, 45·4; H, 6·1%). The infra-red spectrum of a sublimed specimen was identical with that of a sublimed specimen of authentic (+)-methylsuccinic acid.

Chromic Oxide Oxidation of 7-Chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric Acid.—The acid (400 mg.) in acetic acid (2 ml.) was heated on the water-bath with chromic oxide (1·0 g.) in acetic acid (8 ml.) and water (2 ml.). After 10 minutes the reaction mixture was diluted with water and continuously extracted with ether, affording on recovery a greenish solid. Re-extraction with ether gave a colourless solid which sublimed at 60—80°/10^{-3} mm. and, after crystallisation from benzene and resublimation, had m. p. 108—110° (30 mg.). The product did not depress the m. p.s of synthetic (±)- or (+)-methylsuccinic acids or the m. p. of the product obtained in the periodate oxidation (above) (Found : C, 45·3; H, 6·1%; equiv., 64·9. Calc. for $C_5H_8O_4$: C, 45·4; H, 6·1%; equiv., 66). Available quantities of the product were insufficient to determine the optical rotation; however, the infra-red absorption spectrum was identical with that of sublimed synthetic (+)-methylsuccinic acid.

Alkaline Hydrolysis of 7-Chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric Acid.—The acid (0·50 g.) in 3N-sodium hydroxide (15 ml.) was heated under reflux for 2 hours in nitrogen. After acidification with 3N-sulphuric acid, the solution was steam-distilled but no volatile acid was detected in the distillate. The colourless solid (0·35 g.) which separated from the residual solution at 0°, was taken up in ether (solution A), and the insoluble material (20 mg.) rejected. Continuous ether-extraction of the filtrate and recovery furnished a gum which was redissolved in ether (solution B).

Solution A was extracted in turn with 1% aqueous sodium hydrogen carbonate and N-sodium hydroxide, and, on removal of the ether, the neutral fraction remained as a crystalline solid (74 mg.), m. p. 150—155°. After three crystallisations from ethanol it formed colourless prisms of a *dilactone* (VII), m. p. 165—168°. The compound was neutral to the Universal Indicator, and gave no colour with ferric chloride [Found : C, 53·9, 53·9; H, 4·1, 4·4; OMe, 19·5%; *M* (Rast), 298; equiv. (by lactone titration), 153. $C_{14}H_{13}O_6Cl$ requires C, 53·7; H, 4·2; 2OMe, 19·8%; *M*, 312·6; equiv., 156 (for a dilactone)]. Ultra-violet absorption max. : 290 mμ, (log ε 3·25) in methanol. The infra-red spectrum showed two bands in the >C=O region at 1815 and 1795 cm.$^{-1}$ ascribed to five-membered ring $\Delta^{\beta\gamma}$-lactone and unconjugated five-membered ring lactone, respectively.

The bicarbonate extract, after acidification and extraction with ether, furnished a solid (60 mg.), m. p. 165—175° (decomp.), separated by fractional crystallisation from ethyl methyl ketone–light petroleum (b. p. 60—80°) into unchanged starting material and the dibasic acid $C_{13}H_{13}O_6Cl$ (Part II), m. p. 190—198° (decomp.), identified by comparison of the infra-red spectra [Found : C, 51·4; H, 4·5; OMe, 9·8%; equiv., 159. Calc. for $C_{13}H_{13}O_6Cl$: C, 51·9; H, 4·3; 1OMe, 10·3%; equiv., 150 (dibasic acid)].

The sodium hydroxide extract after acidification, extraction with ether, and recovery, afforded a *phenol* (2 mg.), crystallising in colourless needles, m. p. 205—208° (decomp.), from ethyl

acetate and giving a green colour with ferric chloride in ethanol. This substance was not investigated further.

Solution B after extraction with sodium hydrogen carbonate, recovery, and recrystallisation from ethanol yielded needles, m. p. and mixed m. p. with lactone A, $C_{14}H_{13}O_6Cl$ (Part II), 220° (10 mg.). The bicarbonate extract, after acidification and recovery, as before, furnished a mixture (50 mg.), m. p. 158—164° (decomp.), of acidic substances, including starting material, which resisted purification.

A similar yield of the dilactone $C_{14}H_{13}O_6Cl$ was obtained when the time of heating under reflux was 6 hours, but in this case the small acidic fractions appeared homogeneous and consisted of the dibasic acid $C_{13}H_{13}O_6Cl$ only.

Only starting material was recovered when 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric acid was warmed with 40% sodium hydroxide solution for 10 minutes at 60° and then set aside for 48 hours at room temperature.

We are indebted to Mr. H. A. Willis, Imperial Chemical Industries Limited, Plastics Division, for infra-red facilities, and to Miss D. Ismay for assistance in the preparation of the griseofulvin oxidation products.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, BUTTERWICK RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS. [*Received, February 22nd*, 1952.]

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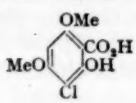
762. *Griseofulvin. Part IV.* Structure.*

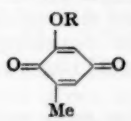
By JOHN FREDERICK GROVE, J. MACMILLAN, T. P. C. MULHOLLAND, and M. A. THOROLD ROGERS.

The structure 7-chloro-4 : 6-dimethoxycoumaran-3-one-2-*spiro*-1′-(2′-methoxy-6′-methyl*cyclo*hex-2′-en-4′-one) (IX; R = Me) accounts for the known physical and chemical properties of griseofulvin and for the degradation products described in Parts I—III (preceding papers).

FROM the oxidative degradations described in Part II (*J.*, 1952, 3958), it was concluded that griseofulvin possesses a benzenoid ring (A) and a hydroaromatic six-membered ring (C) thereby confirming the views of Oxford, Raistrick, and Simonart (*Biochem. J.*, 1939, **33**, 240). The nature and orientation of ring A follows from the formation of 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (I) from griseofulvin by oxidation with zinc permanganate in acetone—conditions which are considered to preclude rearrangement. The aromatic character of ring A is borne out by the lack of reactivity of the chlorine substituent towards aqueous hydrolytic reagents, and towards sodium alkoxides. Thus, griseofulvic acid was recovered unchanged by refluxing 2N-sodium methoxide and, while treatment with N/25-sodium ethoxide replaces a labile methoxyl group by ethoxyl, forming an acidic product, $C_{17}H_{17}O_6Cl$, the chlorine atom survives. Similarly, the two labile methoxyl groups in griseofulvin which are readily hydrolysed with aqueous alkali in the formation of norgriseofulvic acid (Oxford *et al.*, *loc. cit.*) are exchanged for ethoxyl on treatment with N/25-sodium ethoxide; the chlorine atom is however retained in the product $C_{19}H_{21}O_6Cl$.



(I)



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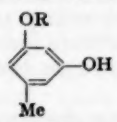

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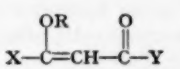
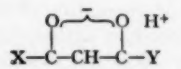


(IV)

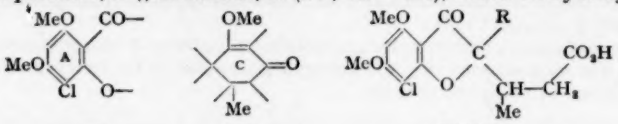


(V)

The presence of a second six-membered ring (C) in griseofulvin is indicated by oxidation with chromic oxide to 3-methoxy-2 : 5-toluquinone (II; R = Me) (Part II) and by formation of orcinol (III; R = H) by potassium hydroxide fusion (Oxford *et al.*, *loc. cit.*). Since the three methoxyl groups in griseofulvin appear in the oxidation products (I) and (II; R = Me), it is evident that griseofulvin is not the methyl ester of a carboxylic acid (contrast Oxford *et al.*, *loc. cit.*; see also Part I). Furthermore, it has been established that the

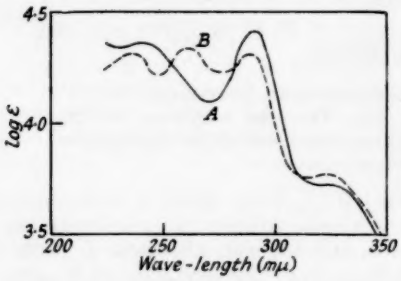
* Part III, preceding paper.

methoxyl group in the quinone (II; R = Me) is derived from a methyl enol ether of the type (IV) (Part I; *J.*, 1952, 3949) as follows. Ethylation of griseofulvic acid with diazoethane or ethanolic hydrogen chloride affords two isomeric ethyl ethers $C_{18}H_{19}O_6Cl$, one of which, of m. p. 205—206°, is oxidised by chromic oxide to 3-ethoxy-2 : 5-toluquinone (II; R = Et), identical with a synthetic specimen. Both ethyl ethers give 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid and 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid on permanganate oxidation. These facts can only be explained by postulating the presence, in griseofulvin, of (IV; R = Me), which on hydrolysis affords the



(VI) (VII) (VIII)

tautomeric system (V) in griseofulvic acid; ethylation of (V) then affords two isomeric ethyl ethers. The second ethyl ether is dimorphous, forms of m. p. 192—193° and 167—168° having been isolated, and like *iso*griseofulvin, does not yield a quinone with chromic oxide. The two ethyl ethers are assigned the normal and the *iso*structure respectively, relative to griseofulvin and *iso*griseofulvin, from a consideration of their ultra-violet absorption spectra [Figure : the band at 262 mμ in the ether, m. p. 192—193°, corresponds



A, Ethyl ether, m. p. 205—206° ($\lambda_{max.}$ 328, 289, 239 mμ; log ε 3·73, 4·41, 4·36 *respectively*).
B, Ethyl ether, m. p. 192—193° ($\lambda_{max.}$ 325, 290, 262, 235 mμ; log ε 3·77, 4·31, 4·34, 4·31 *respectively*).
(*Both in methanol.*)

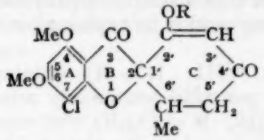
to a similar band in *iso*griseofulvin (Part I)] and because of their behaviour towards chromic oxide oxidation and the lack of carbonyl reactivity in the lower-melting ether which is paralleled in *iso*griseofulvin (Part I).

All the carbon atoms in griseofulvin are accounted for in the oxidation products, 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (I) and 3-methoxy-2 : 5-toluquinone (II; R = Me). That none of them is common to both rings A and C has been demonstrated by cleavage of griseofulvin, in significant yield, into the acid (I) and orcinol monomethyl ether (III; R = Me) by 2N-sodium methoxide (0·5N-sodium methoxide gave anomalous results described in the Experimental section). A similar fission, dealt with in detail in Part VI (*J.*, 1952, 3994), has been encountered in the alkaline hydrolysis of dihydrogriseofulvin which yields the salicylic acid (I) (derived from ring A) and *m*-cresol (from ring C). Moreover, formation of (I) under hydrolytic conditions provides convincing chemical proof that there is a carbonyl group directly attached to the benzenoid ring (A) as suggested by the spectroscopic evidence (Part I).

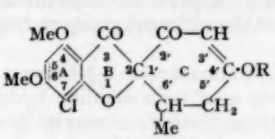
The hydroaromatic ring (C) must contain the *C*-methyl group and the olefinic double bond known to be present in griseofulvin (Part I). Moreover, if it is assumed that rearrangement does not occur in the formation of orcinol (III; R = H) and the monomethyl ether (III; R = Me), two potential hydroxyl groups must be located in the 3 : 5-positions with respect to the *C*-methyl group. Finally, ring C must contain at least the methyl ether group of the system (IV; R = Me). The most likely skeleton of ring C therefore appears to be (VII).

The manner in which the two partial structures (VI) and (VII) are linked in griseofulvin seems to us to be unequivocably determined by the formation of the acids $C_{14}H_{15}O_6Cl$

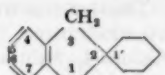
and $C_{14}H_{15}O_7Cl$, which were shown in Parts II and III to be (VIII; R = H and OH respectively). These acids, derived from griseofulvic acid by alkaline peroxide and by permanganate respectively, are substituted coumaran-3-ones in which the carbonyl and oxygen ether bridges from partial structure (VI) are linked to the same carbon atom, adjacent to a *C*-methyl group. Union of partial structures (VI) and (VII) in a like manner leads to the two spiran structures (IX) and (X) which are isomeric methyl ethers of the



(IX)



(X)



(XI)

tautomeric enol (XII) and are therefore considered to represent griseofulvin and *iso*griseofulvin although not necessarily respectively. It is considered that (IX; R = Me) is more likely to give rise to 3-methoxy-2 : 5-toluquinone (II; R = Me) on chromic oxide oxidation and therefore represents griseofulvin. *iso*Griseofulvin, on the other hand, does not yield a quinone with chromic oxide (Part II) and is therefore considered to be (X; R = Me): the *o*-quinone which structure (X) might be expected to yield has not been isolated; it probably does not survive the oxidation. A conclusive decision that (IX; R = Me) and (X; R = Me) represent griseofulvin and *iso*griseofulvin respectively follows independently from hydrogenation studies (see Part VI).

The conclusion that griseofulvin is 7-chloro-4 : 6-dimethoxycoumaran-3-one-2-*spiro*-1′-(2′-methoxy-6′-methyl*cyclo*hex-2′-en-4′-one) (IX; R = Me) has already been briefly reported (Grove, Ismay, MacMillan, Mulholland, and Rogers, *Chem. and Ind.*, 1951, 219); *iso*griseofulvin is 7-chloro-4 : 6-dimethoxycoumaran-3-one-2-*spiro*-1′-(4′-methoxy-6′-methyl *cyclo*hex-3′-en-2′-one) (X; R = Me). There are difficulties inherent in the old nomenclature (Oxford *et al.*, *loc. cit.*) based on griseofulvic acid (which is not a carboxylic acid) which apply particularly to its ethers and reduction products; a nomenclature is required which will denote these derivatives unambiguously and will also be applicable to analogues (to be described later) throughout the griseofulvin chemistry. After consultation with the Editor, we propose the name grisan, for the ring system (XI). The new names corresponding to the old ones are given in the Table, but the trivial name griseofulvin will be retained. The neutral compound $C_{15}H_{15}O_4Cl$, a product of the alkaline hydrolysis of griseofulvin, is shown below to be a substituted tetrahydrodibenzfuran and not a derivative of grisan, and the trivial name decarboxygriseofulvic acid introduced for this compound by Oxford *et al.* will therefore be abandoned in future publications.

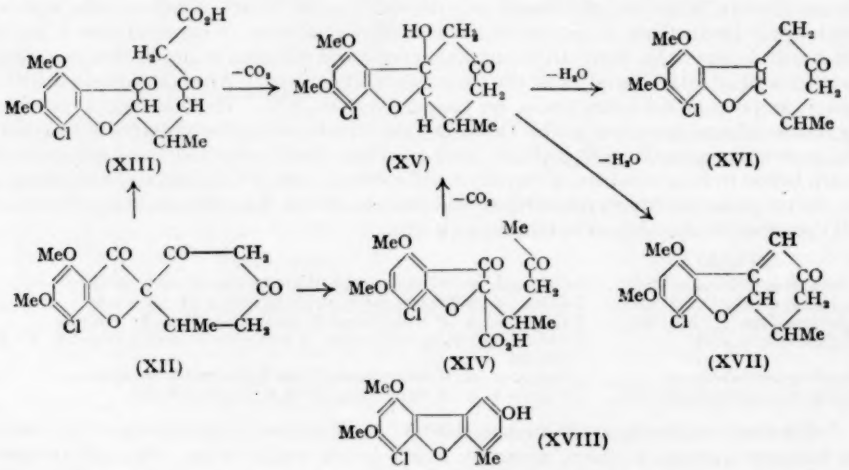
Old name	New name
Griseofulvin (IX; R = Me) ...	7-Chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione.
Griseofulvic acid (XII)	7-Chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione.
*iso*Griseofulvin (X; R = Me)...	7-Chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione.
Norgriseofulvic acid	7-Chloro-4(or 6)-hydroxy-6(or 4)-methoxy-2′-methylgrisan-3 : 4′ : 6′-trione.
Dihydrogriseofulvin	7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione.
Tetrahydrodeoxygriseofulvin	7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one.

7-Chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione (XII), of which (IX) and (X) are isomeric monoenol ethers, normally exists in the enolic form. As such it may be regarded as a derivative of dihydroresorcinol and the observed p*K* of 4·5 may be compared with the p*K*'s of dimedone and dihydroresorcinol found by Schwarzenbach and Lutz (*Helv. Chim. Acta*, 1940, **23**, 1162) to fall close to 5·2. Strongly acidic enols are known to react readily with diazomethane with exclusive formation of the enol ether (Eistert, "Newer Methods of Preparative Organic Chemistry," Interscience Publ. Inc., New York, 1948, p. 528). Nevertheless, the method has been little used for the preparation of the enol ethers of cyclic 1 : 3-diketones. We find that the cyclic 1 : 3-diketones dimedone and dihydroresorcinol react smoothly with diazomethane, and the enol ethers obtained are readily hydrolysed (see also Euler and Hasselquist, *Rec. Trav. chim.*, 1950, **69**, 402).

Structure (IX; R = Me) satisfactorily accords with all the known physical and chemical properties of griseofulvin. It is consistent with the ultra-violet and infra-red spectroscopic evidence, and with the high optical rotation of griseofulvin and its hydrolysis products, which contain the αβ-unsaturated ketone system of high polarisability attached to the *spiro*-carbon atom. A second asymmetric carbon atom is also present (in the 6'-position in griseofulvin) and is responsible for the small negative rotations of decarboxygriseofulvic acid and of the C_{14} oxidation products, and finally appears in the periodate fission product (+)-methylsuccinic acid. The non-reactivity of the carbonyl group in ring B may readily be explained in terms of steric hindrance.

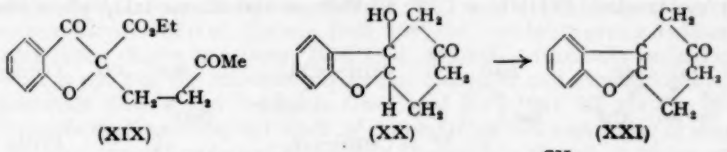
7-Chloro-4 : 6-dimethoxycoumaranone-2-β-butyric acid (VIII; R = H), obtained in the oxidation of griseofulvic acid with alkaline hydrogen peroxide presumably arises by decarboxylation of the intermediate dicarboxylic acid (VIII; R = CO_2H), the expected product of the oxidation by alkaline hydrogen peroxide or hypobromite of the dihydroresorcinol ring C. 7-Chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric acid, one of the permanganate oxidation products of griseofulvin, undoubtedly results from a similar reaction sequence, set out in detail in Part II, in which the intermediate product (VIII; R = H) is oxidised at the activated methine group to the corresponding tertiary alcohol (VIII; R = OH); this must also occur in the alkaline hypobromite oxidation (cf. Beckmann, *Ber.*, 1950, **83**, 315).

The structure and mode of formation of decarboxygriseofulvic acid, one product of aqueous alkaline hydrolysis of griseofulvin, may be deduced as follows. Ultra-violet spectroscopy suggests that a gross molecular rearrangement is involved, and in particular that the partial structure (VI) is absent in the latter compound (Part I). Moreover, in Part II it was shown that decarboxygriseofulvic acid is almost certainly a partially hydrogenated dibenzofuran. It is therefore considered that decarboxygriseofulvic acid is formed by the reactions (XII ⟶ XIII ⟶ XV ⟶ XVI) or (XII ⟶ XIV ⟶ XV ⟶ XVI). The alternative intermediates (XIII) or (XIV) undergo internal Knoevenagel condensation

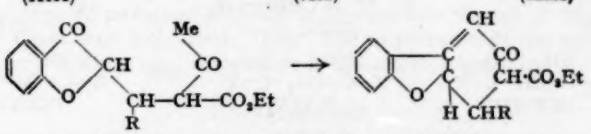


between the otherwise unreactive coumaranone carbonyl group and an activated methylene group, with simultaneous decarboxylation; liberation of carbon dioxide during the reaction has been demonstrated experimentally. The aldol intermediate (XV) may lose a molecule of water in two ways, to give the tetrahydrodibenzofuran (XVI) or (XVII). The ultra-violet spectrum of decarboxygriseofulvic acid (Part I) is consistent only with (XVI). On this basis the phenol $C_{15}H_{13}O_4Cl$ is (XVIII), and its formation from (XII) by yellow mercuric oxide in alkali (Part II) is simply a dehydrogenation of the intermediate substituted tetrahydrodibenzofuran. "*iso*Decarboxygriseofulvic acid," formed in small

yield with decarboxygriseofulvic acid (Part I), is considered to be the alternative dehydration product (XVII); this is confirmed by the ultra-violet absorption curve ($\lambda_{max.}$ 342 mμ; log ε 4·38) which is typical of a compound containing an αβ-unsaturated keto-group conjugated with an aromatic ring, and by the infra-red spectrum which shows the carbonyl group to be conjugated (strong bands at 1670 and 1610 cm.$^{-1}$) [the keto-grouping in (XVI) absorbs at 1710 cm.$^{-1}$ (Part I)]. It may be recalled that (XVII) is the structure proposed for decarboxygriseofulvic acid by Oxford *et al.* (*loc. cit.*). It is formed in small yield when decarboxygriseofulvic acid is heated with methanolic sodium hydroxide in an atmosphere of nitrogen.



(XIX) (XX) (XXI)



(XXII) (R = *p*-MeO·C_6H_4) (XXIII)

Considerable support for the postulated rearrangement of (XII) to the substituted tetrahydrodibenzofurans (XVI) and (XVII) comes from Henecka's observation (*Ber.*, 1949, **81**, 197) that ethyl 2-3′-ketobutyl-3-ketocoumaran-2-carboxylate (XIX) affords the aldol condensation product (XX) with dilute mineral acid and the tetrahydrodibenzofuran (XXI) with aqueous sodium hydroxide, and from the report by Panse, Shah, and Wheeler (*J. Indian Chem. Soc.*, 1941, **18**, 453) that (XXII) under the influence of aqueous alkali affords the dibenzofuran derivative (XXIII) although the αβ-unsaturated ketone nature of this product was not proved.

Grove and McGowan's observation (*Nature*, 1947, **160**, 574) that (XVI) showed basic properties, forming a complex with ferric chloride has been re-investigated. It has been found that the complex is not a simple ferrichloride and analytical data suggest that it is a complex of the type $[BH]^+_2\,FeCl_4^{--}$. It is not hygroscopic but is decomposed by warm water with the formation of (XVII) in high yield. (XVII) does not reform the complex on treatment with ferric chloride in glacial acetic acid and the detailed mechanism involved in the overall rearrangement (XVI ⟶ XVII) is not understood.

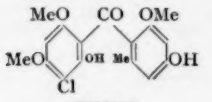
The extreme lability of one of the aromatic ether groups in griseofulvin towards aqueous 0·5N-sodium hydroxide is surprising but finds an analogy in the hydrolysis of alizarin 1-methyl ether with barium hydroxide (Perkin, *J.*, 1907, **91**, 2069). In view of the well-known reactivity of a methoxyl group in the *ortho*-position to a carbonyl group, it is probably the 4- rather than the 6-methoxyl group which is hydrolysed.

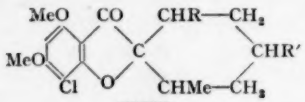
The behaviour of griseofulvin and 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione towards sodium alkoxides, described above, substantiates this lability of the ether linkages and the compounds $C_{17}H_{17}O_6Cl$ and $C_{19}H_{21}O_6Cl$ are 7-chloro-4(or 6)-ethoxy-6(or 4)-methoxy-2′-methylgrisan-3 : 4′ : 6′-trione and 7-chloro-4(or 6) : 2′-diethoxy-6(or 4)-methoxygris-2′-en-3 : 4′-dione, respectively.

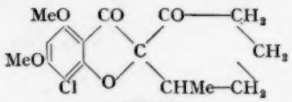
" Decarboxynorgriseofulvic acid " has not been obtained from the alkaline hydrolysis of griseofulvin. The compound (XVI) does not contain the ester vinylogue structure present in the 4-methoxycoumaranone portion of griseofulvin; that the rather unusual hydrolysis of the aryl ether group should fail to proceed once the rearrangement to the tetrahydrodibenzofuran structure has taken place is therefore less surprising than that 7-chloro-4(or 6)-hydroxy-6(or 4)-methoxy-2′-methylgrisan-3 : 4′ : 6′-trione should apparently resist rearrangement. It is conceivable that the structure is stabilised by chelation from a hydroxy-substituent in the 4-position; alternatively, it is possible that the break-down products have merely evaded isolation.

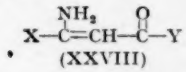
Griseofulvin (IX; R = Me) may be regarded as the vinylogue of a 1 : 3-diketone and therefore susceptible to fission under alkaline conditions. In the cleavage of griseofulvin with 2N-sodium methoxide, fission of the $C_{(2)}$–$C_{(3)}$ bond in the coumaranone ring must occur before, or at the same time as, hydrolysis of the ether linkage, otherwise formation of the benzophenone (XXIV) might be expected and no evidence of this was obtained. It is not clear why the sodium salt of the salicylic acid (I) was isolated in this reaction and not the methyl ester, although rigorous exclusion of water was not attempted.

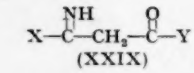
Aqueous alkaline hydrolysis does not yield the salicylic acid (I) by fission of the 1 : 3-diketone vinylogue structure because after hydrolysis of the enolic ether system (IV; R = Me) the product (XII) is a 1 : 3 : 5-triketone and fission takes place more easily elsewhere.

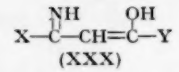

(XXIV)


(XXV)

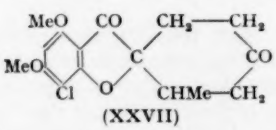

(XXVI)

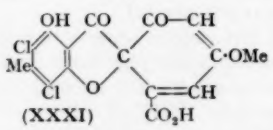

(XXVIII)


(XXIX)


(XXX)

Products A and C of the catalytic reduction of (XII) (Part I) are 7-chloro-4′ : 6′-dihydroxy-4 : 6-dimethoxy-2′-methylgrisan-3-one (XXV; R = R′ = OH) and 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one (XXV; R = R′ = H) respectively, while product B is considered to be (XXV; R = OH, R′ = H) rather than (XXV; R = H, R′ = OH) since the ketone obtained by chromic oxide oxidation is shown in Part VI to be the 1 : 3-diketone (XXVI) and not (XXVII). The reduction of 1 : 3-diketones to the corresponding dihydric and monohydric secondary alcohols and finally to the saturated hydrocarbon has many analogies in the literature.


(XXVII)


(XXXI)

The reaction of griseofulvin with methanolic ammonia (Part I) is typical of αβ-unsaturated β-alkoxy-ketones and 1 : 3-diketones (see Cromwell, *Chem. Reviews*, 1946, **38**, 83). The basic product, $C_{16}H_{16}O_5NCl,H_2O$, may possess either the amino- (XXVIII) or the imino-structure (XXIX ⇌ XXX), both of which have been proposed for the amino-derivatives of open-chain 1 : 3-diketones (Combes and Combes, *Bull. Soc. chim.*, 1892, **7**, 778; Rugheimer, *Ber.*, 1916, **47**, 2759). However, the wine-red ferric chloride colour given by the griseofulvin derivative and the amino-derivatives of several *cyclo*hexane-1 : 3-diones, prepared for comparison, is not readily accounted for by incorporating either (XXVIII), (XXIX), or (XXX) into the more rigid *cyclo*hexane ring. Moreover, the infra-red absorption spectra of the cyclic 1 : 3-diketone derivatives are difficult to interpret (cf. Cromwell *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 3337). This aspect is at present being investigated in these laboratories.

In conclusion, it is interesting that the spiran structures (IX and X; R = Me) proposed for griseofulvin and *iso*griseofulvin respectively, closely resemble one of the structures (XXXI) suggested for the chlorine-containing mould product, erdin, by Calam, Clutterbuck, Oxford, and Raistrick (*Biochem. J.*, 1947, **41**, 458). However, the properties of griseofulvin and *iso*griseofulvin on the one hand and erdin on the other are dissimilar. Catalytic reduction of erdin splits the oxygen bridge with the formation of a substituted benzophenone, while 80% sulphuric acid (as in the case of many hydroxybenzophenones) splits the carbonyl link. The ether linkage in the coumaranone ring of griseofulvin is stable to catalytic reduction. Treatment of griseofulvin with 80% sulphuric acid gives, first,

7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione and then at higher temperatures 2 mols. of carbon dioxide are evolved with the production of much tar.

Structure (IX; R = Me) possesses two features which are rather uncommon in a natural product, namely, the aromatic chlorine substituent and the spiran structure. Since the isolation by Raistrick and co-workers of griseofulvin, geodin, erdin, and caldariomycin (Clutterbuck, Mukhopadhyay, Oxford, and Raistrick, *Biochem. J.*, 1940, **34**, 664) a number of chlorine-containing mould metabolic products have been described including sclerotiorine (Curtin and Reilly, *Biochem. J.*, 1940, **34**, 1419), a series of compounds from *Aspergillus ustus* (Hogeboom and Craig, *J. Biol. Chem.*, 1946, **162**, 363; Doering, Dubos, Noyce, and Dreyfus, *J. Amer. Chem. Soc.*, 1946, **68**, 725), and the antibiotics chloramphenicol and aureomycin (Broschard *et al.*, *Science*, 1949, **109**, 199), the latter giving 5-chlorosalicylic acid on degradation (Kühn and Dury, *Ber.*, 1951, **84**, 563). Naturally occurring spirans are somewhat rarer, but the steroidal sapogenins diosgenin and sarsasapogenin and the alkaloid gelsemine (Gibson and Robinson, *Chem. and Ind.*, 1951, 93) may be mentioned. 4 : 6 : 2′-Trimethoxy-6′-methylgris-2′-en-3 : 4′-dione, the dechloro-analogue of griseofulvin, produces the same type of biological response in *Botrytis allii* though at higher concentrations (MacMillan, *Chem. and Ind.*, 1951, 719). The importance of the spiro-structure in conferring " curling " activity on the molecule is under investigation.

Experimental

M. p.s are corrected. Microanalyses are by Drs. Strauss and Weiler, Oxford (who also obtained some of the ultra-violet absorption spectra) and by Mr. W. Brown. Infra-red spectra were obtained as described in Part I.

Ethylation of 7-Chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione (Griseofulvic Acid).—(a) *With ethanolic hydrogen chloride.* A suspension of griseofulvin (2·5 g.) in absolute ethanol (200 ml.) was saturated with dry hydrogen chloride and then heated under reflux for 2 hours. After removal of most of the solvent *in vacuo*, the residue was poured into ice-water. The precipitate was collected, washed with sodium carbonate and water, dried, and crystallised from alcohol, giving a solid (0·4 g.), m. p. 164—166°. The residue obtained from the mother-liquor on evaporation was extracted with hot benzene (60 ml.). The benzene solution was separated from insoluble material and chromatographed on acid-washed alumina (20 × 2·5 cm.). Elution with ether +1% of methanol gave the following bands (identified in ultra-violet light) : (i) violet, which gave a colourless solid (30 mg.), m. p. 182—185°, raised by crystallisation from methanol to 197—205°; (ii) violet, not completely separated from (i); and (iii) blue-violet, giving an oil which yielded a solid (0·07 g.), m. p. 202—203°. Fraction (ii) yielded a colourless solid (0·6 g.), m. p. 166°, and a colourless solid which after crystallisation from ethanol had m. p. 147—180° and was rechromatographed giving two further fractions (0·15 g.), m. p. 163—165° and (0·06 g.), m. p. 200°. The combined fractions of m. p. 163—166° crystallised from ethanol in colourless prisms or short needles, m. p. 167—168°, of *7-chloro-4′-ethoxy-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione* (X; R = Et). When seeded with the higher-melting form [see (*b*) below], it crystallised in long needles, m. p. 192—193°, $[\alpha]_D^{20}$ +214° (*c*, 0·98 in acetone) (Found : C, 58·8; H, 5·0; Cl, 9·8. $C_{18}H_{19}O_6Cl$ requires C, 58·8; H, 5·2; Cl, 9·7%).

The fractions of m. p. 200—203°, *7-chloro-2′-ethoxy-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione* (IX; R = Et), crystallised from ethanol as colourless needles or prisms, m. p. 205—206°, $[\alpha]_D^{20}$ +316° (*c*, 0·98 in acetone) (Found : C, 59·0; H, 5·2; Cl, 10·1%). It was less soluble in ethanol than its isomer.

(b) *With diazoethane.* 7-Chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione (3·0 g.), suspended in ether, was treated with excess of ethereal diazoethane (Adamson and Kenner, *J.*, 1937, 1551). After 24 hours at 0°, unchanged material (1·15 g.) was removed by filtration. The gum obtained on evaporation was chromatographed in benzene (20 ml.) on acid-washed alumina (20·0 × 2·5 cm.). Elution was followed in ultra-violet light and gave two violet bands. Elution of the first with ether +0·5% of methanol gave 7-chloro-4′-ethoxy-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione (X; R = Et) (0·73 g.), long blunt-ended needles (from ethanol), m. p. 192°. A mixed m. p. with the form, m. p. 168°, obtained as in (*a*) above, melted sharply at 192°. Elution of the second with ether +2% of methanol gave the isomer (IX; R = Et) (0·54 g.), m. p. and mixed m. p. with a specimen obtained as in (*a*), 203°.

(c) *With ethanol.* 7-Chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione (102 mg.), heated under reflux for 6 hours with absolute ethanol (10 ml.), gave unchanged starting material

(50 mg.) and a little 7-chloro-4′-ethoxy-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione (X; R = Et), m. p. 188°. None of the 2′-ethoxy-isomer (IX; R = Et) was isolated in this experiment.

Oxidation of 7-Chloro-2′-ethoxy-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione (IX; R = Et). (a) *With chromic oxide.* A warm solution of (IX; R = Et) (366 mg.) in acetic acid (8 ml.) was treated in portions with chromic oxide (1·0 g.) in acetic acid (7 ml.) and water (2·2 ml.). After the vigorous reaction had moderated, the mixture was heated under reflux for 20 minutes, cooled, diluted with water (25 ml.), and extracted with benzene. The brown oil, obtained on recovery, was sublimed *in vacuo* at room temperature, giving a yellow solid with a trace of gum. After being pressed on a porous plate, it crystallised from ether–light petroleum in long yellow needles, m. p. and mixed m. p. with a synthetic specimen of 3-ethoxy-2 : 5-toluquinone, 54—56°. Sublimation at 45° gave a little more of the quinone (total, 5 mg.), greatly contaminated with brown oil.

Trituration of the non-volatile residue with ether gave starting material, m. p. and mixed m. p. 203°.

(b) *With potassium permanganate.* Treatment of (IX; R = Et) (150 mg.) in acetone (50 ml.) with powdered potassium permanganate (0·6 g.) as described by Oxford *et al.* (*loc. cit.*) for the permanganate oxidation of griseofulvin gave 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (31 mg.), m. p. and mixed m. p. 220—222°, together with 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric acid (8 mg.), m. p. 186—189° (decomp.), identified by mixed m. p. and infra-red spectra.

Oxidation of 7-Chloro-4′-ethoxy-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione (X; R = Et).—(a) *With chromic oxide.* A warm solution of (X; R = Et) (379 mg., 1 millimol.) in acetic acid (8 ml.) was treated in portions with chromic acid (1·05 g.) in acetic acid (7 ml.) and water (2·2 ml.), as described above. Working up in the same manner gave a colourless sublimate melting indefinitely at *ca.* 130° and a little unchanged starting material, m. p. and mixed m. p. 189°. Further extraction of the diluted reaction mixture, continuously with benzene for 3 days, gave a dark gum (60 mg.) which was sublimed *in vacuo* at 50°. Some brown oil was obtained which very slowly crystallised in ether. The crystals consisted mainly of small colourless needles of starting material but included one diamond-shaped, yellow crystal, m. p. 117—119°. No 3-ethoxy-2 : 5-toluquinone was obtained.

(b) *With potassium permanganate.* Treatment of (X; R = Et) (230 mg.) in acetone (60 ml.) with powdered potassium permanganate (0·95 g.) as above gave 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (37 mg.), m. p. and mixed m. p. 220—222°, and 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaranone-2-β-butyric acid (2 mg.), m. p. 172—175°, identified by mixed m. p. and comparison of the infra-red spectra.

Iron Complex formed by 8-Chloro-1 : 2 : 3 : 4-tetrahydro-3-keto-5 : 7-dimethoxy-1-methyldibenzofuran (XVI).—8-Chloro-1 : 2 : 3 : 4-tetrahydro-3-keto-5 : 7-dimethoxy-1-methyldibenzofuran (XVI) (10 mg.) was dissolved in glacial acetic acid (5 ml.), and anhydrous ferric chloride (30 mg.) in concentrated hydrochloric acid (0·5 ml). added. After a few minutes the *complex* crystallised and was filtered, washed with a little glacial acetic acid, and dried *in vacuo* at room temperature for 1 week over phosphoric oxide and potassium hydroxide [Found : C, 45·7; H, 4·1; Fe, 7·3; Cl (total), 27·9; Cl (ionic), 17·7. $(C_{15}H_{15}O_4Cl)_2,FeCl_2,2HCl$ requires C, 45·6; H, 4·1; Fe, 7·1; Cl (total), 27·0; Cl (ionic), 18·0%]. The complex sintered at 160° but did not melt at 300°. It was readily soluble in glacial acetic acid. It was decomposed by warm water with the production of a colourless solid (see below); the aqueous mother-liquor contained both Fe^{+++} and Fe^{++}.

8-Chloro-1 : 2 : 3 : 9-tetrahydro-3-keto-5 : 7-dimethoxy-1-methyldibenzofuran (XVII).—The iron complex from the tetrahydrodibenzfuran (XVI) (90 mg.) was decomposed by hot water, and the crude product (72 mg.), m. p. 152—170°, in benzene (5 ml.) was chromatographed on alumina (pH 4; Grade II). Elution with benzene was followed in ultra-violet light and gave (i) a lower greyish-green fluorescent band which gave starting material (XVI) (20 mg.), m. p. and mixed m. p. 136°, and (ii) a yellow fluorescent band which yielded a colourless solid (45 mg.). After crystallisation from benzene the latter formed *8-chloro-1 : 2 : 3 : 9-tetrahydro-3-keto-5 : 7-dimethoxy-1-methyldibenzofuran* as prisms, m. p. 209—210°, undepressed on admixture with the "*iso*decarboxygriseofulvic acid" obtained in the alkaline hydrolysis of griseofulvin in Part I, and depressed below 180° by the phenol (XVIII) [Found : C, 61·3; H, 5·2; Cl, 12·7%; *M* (Rast), 277. $C_{15}H_{15}O_4Cl$ requires C, 61·1; H, 5·1; Cl, 12·0%; *M*, 295). Ultra-violet absorption max. in methanol : 342, 250 mμ (log ε 4·38, 4·00). It did not re-form the complex on treatment with ferric chloride and gave an orange colour, unchanged at 100°, with concentrated sulphuric acid.

Hydrolysis of Griseofulvin with Barium Hydroxide. Griseofulvin (1·0 g.) and saturated barium hydroxide solution (100 ml.) were heated under reflux for 5 hours (soda-lime guard tube). The crystals gradually disappeared, and a microcrystalline precipitate was formed. This precipitate was rapidly filtered, washed, and extracted with ethanol in a Soxhlet apparatus. The residue was identified as barium carbonate. The extract, on evaporation, gave 8-chloro-1 : 2 : 3 : 4-tetrahydro-3-keto-5 : 7-dimethoxy-1-methyldibenzofuran (XVI) (0·12 g.), long needles (from 50% methanol), m. p. 135·5—137°.

Hydrolysis of 8-Chloro-1 : 2 : 3 : 4-tetrahydro-3-keto-5 : 7-dimethoxy-1-methyldibenzofuran.—The ketone (XVI), m. p. 137° (22 mg.), and boiled N-sodium hydroxide (0·4 ml.) were heated under reflux for 3 hours in nitrogen with enough methanol to yield a homogeneous solution. The solid (15 mg.), m. p. 142—158°, which separated at 0°, was chromatographed in benzene on alumina (pH 4; Grade II) and eluted with benzene. The lower band, fluorescing greenish-grey (ultra-violet), yielded unchanged starting material, m. p. 137° (7 mg.). The upper band, fluorescing yellow, yielded a colourless solid, m. p. 209—210° (0·6 mg.) not depressed by admixture with 8-chloro-1 : 2 : 3 : 9-tetrahydro-3-keto-5 : 7-dimethoxy-1-methyldibenzofuran (XVII).

Orcinol Monoethyl Ether.—This was prepared from orcinol (72 g.), ethyl sulphate, and alkali as described by Henrich and Nachtigall for the monomethyl ether (*Ber.*, 1903, **36**, 889). The alkali-insoluble fraction was distilled at 95—110°/4 × 10^{-2} mm., giving orcinol diethyl ether (11·5 g.). The alkali-soluble product was distilled at 110—120°/10^{-2} mm., giving a yellow oil (46 g.) which was absorbed on alumina (pH 4; Grade II) (21·0 × 3 cm.) from its ether solution (450 ml.). Elution with ether, followed in ultra-violet light, gave a narrow yellow band not completely separated from a pale blue fluorescent band. These were collected together (eluate I) and an upper, blue fluorescent band collected separately (eluate II). Eluate I gave a yellow oil which was redistilled at 117—124°/5 × 10^{-2} mm., giving a viscous yellow oil (40 g.) which partly crystallised on long storage. A specimen, pressed on a porous tile, crystallised from light petroleum (b. p. 40—60°) in long colourless needles, m. p. 47°. (Found: C, 71·0; H, 7·85. Calc. for $C_9H_{12}O_2$: C, 71·0; H, 7·9%). Orcinol monoethyl ether is described as an oil, b. p. 265—270°, by Henrich (*Monatsh.*, 1901, **22**, 251). The oily, partly crystalline distillate was used directly in the nitration (see below).

Eluate II gave unchanged orcinol (3·0 g.), m. p. and mixed m. p. 103—106°.

Nitration of Orcinol Monoethyl Ether.—The monoethyl ether (20 g.) in ether (600 ml.) was stirred mechanically and treated dropwise at −4° with nitric acid (10 g.; *d* 1·5). The mixture was then stirred for 1 hour, heated under reflux for 40 minutes, cooled, and washed with water. Recovery of the ethereal layer yielded an oil which was steam-distilled. The volatile fraction, recovered in ether, was absorbed on alumina (pH 4; Grade II) (16 × 2·0 cm.) from its benzene solution (100 ml.) and elution with benzene continued until a dark-brown band reached the bottom of the column. Evaporation of the eluate gave an oil which after several crystallisations from light petroleum (b. p. 40—60°) gave 5-ethoxy-3-hydroxy-2-nitrotoluene in yellow needles (1·3 g.), m. p. 52—53° (Found: C, 54·55; H, 5·6; N, 7·1. Calc. for $C_9H_{11}O_4N$: C, 54·8; H, 5·6; N, 7·1%). Weselsky and Benedikt (*Monatsh.*, 1881, **2**, 370) give m. p. 54°.

The non-volatile residue was extracted with hot benzene and the cooled extract chromatographed on alumina (28 × 3·0 cm.) (pH 4; grade II). Elution with benzene gave the following fractions: (i) Dark yellow-red eluate. Recovery gave a dark oil which after repeated crystallisation from benzene gave 3-ethoxy-5-hydroxy-2-nitrotoluene in yellow needles (1·1 g.), m. p. 114—115° (Found: C, 55·0; H, 5·6; N, 7·1%). It gave no colour with ferric chloride or Gibbs' reagent. Weselsky and Benedikt (*loc. cit.*) give m. p. 103°; the lower value may be due to contamination of their product with a second non-steam-volatile product, described below. (ii) Clear yellow eluate. Crystallisation of the recovered gum from benzene gave yellow needles (0·3 g.), m. p. 118—119°, depressed on admixture with 3-ethoxy-5-hydroxy-2-nitrotoluene (Found: C, 49·8; H, 4·05; N, 7·1. Calc. for $C_7H_7O_4N$: C, 49·7; H, 4·2; N, 8·3%). Analyses and properties suggested this product was 2-nitro-orcinol, described by Henrich and Meyer (*Ber.*, 1903, **36**, 886) as a non-steam-volatile compound, m. p. 122°.

3-Ethoxy-2 : 5-toluquinone.—3-Ethoxy-5-hydroxy-2-nitrotoluene (0·2 g.) in ethanol (20 ml.) was reduced with Raney nickel at room temperature and pressure in the usual way. On the addition of 3N-hydrochloric acid (5 ml.) to the crude product, an almost colourless solid separated but was not isolated. Sulphuric acid (1·5 g.) in water (10 ml.) was added and the mixture treated dropwise with a solution of sodium dichromate (0·6 g.) in water (8 ml.) at 0°. After 12 hours at 0°, a trace of tar was filtered off. Extraction of the filtrate and recovery gave a dark oil which solidified in light petroleum at 0° (50 mg.). Several crystallisations from light

petroleum (b. p. 40—60°) afforded 3-*ethoxy*-2 : 5-*toluquinone*, yellow needles, m. p. 56—58°, which did not depress the m. p. of the quinone of m. p. 54—56° obtained by oxidation of 7-chloro-2′-ethoxy-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione (IX; R = Et) (Found: C, 64·95; H, 5·9. $C_9H_{10}O_3$ requires: C, 65·0; H, 6·1%). 3-Ethoxy-2 : 5-toluquinone gave a green colour with concentrated sulphuric acid. It gradually discoloured.

Hydrolysis of Griseofulvin with 80% *Sulphuric Acid.*—Griseofulvin (500 mg.) in concentrated sulphuric acid (10 ml.) and water (5 ml.) was heated at 150—160° in a stream of carbon dioxide-free nitrogen until evolution of carbon dioxide ceased (40 minutes). The evolved carbon dioxide, trapped in standard baryta, corresponded to 2 mols. per mol. of griseofulvin. The cooled reaction mixture, diluted with water (10 ml.), gave a black solid (330 mg.) which could not be purified.

Alcoholysis of 7-*Chloro*-4 : 6-*dimethoxy*-2′-*methylgrisan*-3 : 4′ : 6′-*trione.*—(a) *Sodium methoxide.* The trione (0·5 g.) was recovered unchanged after 2 hours' heating under reflux with sodium (2·3 g.) in methanol (50 ml.). (b) *Sodium ethoxide.* The trione (0·5 g.) was heated under reflux for 5 hours with sodium (0·55 g.) in absolute ethanol (50 ml.). Dilution of the cooled solution with water, removal of the alcohol *in vacuo*, and acidification gave 7-*chloro*-4(or 6)-*ethoxy*-6(*or* 4)-*methoxy*-2′-*methylgrisan*-3 : 4′ : 6′-*trione* (0·46 g.), m. p. 214—215° (decomp.) (softening at 206°); it crystallised from methanol in colourless prisms, m. p. (dependent on the rate of heating) 234—236° (decomp.) [Found, on a sample dried at 110° over P_2O_5: C, 57·8, 58·4; H, 4·95, 4·9; Cl, 9·95; (OMe)(OEt), 21·1. $C_{17}H_{17}O_6Cl$ requires C, 57·85; H, 4·85; Cl, 10·06; (OMe)(OEt), 21·6%]. Ultra-violet absorption max. in methanol: ~330, 289 mμ (log ε 3·81, 4·67).

Action of Sodium Ethoxide on Griseofulvin.—(a) *With* ca. N/25-*sodium ethoxide.* Griseofulvin (1·0 g.) was heated under reflux for 5 hours with sodium (0·4 g.) in absolute ethanol (400 ml.). Dilution with water, acidification, and removal of the ethanol *in vacuo* gave a solid which was adsorbed on acid-washed alumina (activated at 250°) from its benzene solution. The band fluorescing violet in ultra-violet light was eluted with benzene + 1% of methanol. Recovery gave 7-*chloro*-4 : 2′(*or* 6 : 2′)-*diethoxy*-6(*or* 4)-*methoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* which crystallised from methanol and had m. p. 198—203·5°. It was dried at 110° for 1½ hours over phosphoric oxide [Found: C, 59·45; H, 5·3; Cl, 9·02; (OMe)(OEt)$_2$, 31·7. $C_{19}H_{21}O_6Cl$ requires C, 59·9; H, 5·5; Cl, 9·35; (OMe)(OEt)$_2$, 31·8%]. Ultra-violet absorption max. in methanol: 325, 291, ~254, 237 mμ (log ε 3·82, 4·39, 4·20, 4·42).

(b) *With* ca. 0·5N-*sodium ethoxide.* Griseofulvin (2·0 g.) was heated under reflux for 5 hours with sodium (2·28 g.) in absolute ethanol (200 ml.). Dilution with water (200 ml.) and acidification gave a sticky precipitate which was recovered in ether, giving some gummy crystals (0·23 g.). Removal of the gum by washing with methanol followed by recrystallisation from aqueous methanol gave an impure solid, m. p. 212—214° (decomp.) which resisted further purification. The *X*-ray powder pattern showed it to contain 7-chloro-4 (or 6)-ethoxy-6 (or 4)-methoxy-2′-methylgrisan-3 : 4′ : 6′-trione and was consistent with the presence of some 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid which would account for its violet ferric chloride colour reaction.

The gum, obtained by evaporation of the methanol solution, was dissolved in chloroform and extracted with potassium hydrogen carbonate solution. Acidification gave a resinous solid (1·2 g.), m. p. 125—145° (decomp.), which gave a violet colour with ferric chloride but resisted all attempts at purification.

The reaction was much cleaner when conducted in nitrogen although the only compound isolated was 7-chloro-4(or 6)-ethoxy-6(or 4)-methoxy-2′-methylgrisan-3 : 4′ : 6′-trione, identified by the *X*-ray powder pattern.

Action of 2N-*Sodium Methoxide on Griseofulvin.*—Griseofulvin (0·20 g.) and 2N-sodium methoxide in methanol (20 ml.) were heated under reflux for 5 hours (separation of crystalline material). The cooled mixture was poured into water, and the clear aqueous solution was acidified, precipitating 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (100 mg.) as a white crystalline solid, m. p. 207—208°, raised to 212° (decomp.) by crystallisation from ethyl acetate, and identical with an authentic specimen. Extraction of the aqueous mother-liquors with ether and recovery gave an oil which was distilled *in vacuo*. The oily distillate, crystallised from 1 : 9-benzene–light petroleum, had m. p. 54—59° (*ca.* 8 mg., 10%) and did not depress the m. p. of an authentic sample of orcinol monomethyl ether (Found: C, 69·6; H, 7·05%).

Action of 0·5N-*Sodium Methoxide on Griseofulvin.*—Griseofulvin (2·0 g.) and a solution of sodium (2·28 g.) in methanol (200 ml.) were heated under reflux for 5 hours, cooled, diluted with ice-water (200 ml.), and kept for several hours. The precipitate was dried at 100° (1·76 g.), m. p. 238—240°; it formed clusters of small hard prisms (from toluene or toluene–light petroleum), m. p. 239—240°, $[\alpha]_D^{23}$ +155° (*c*, 1·378 in chloroform) [Found: C, 56·8, 57·0, 56·95; H, 4·4, 4·5,

4·9; Cl, 9·55, 9·4; OMe, 24·4, 24·0%; *M* (Rast), 348. $C_{18}H_{19}O_7Cl$ requires C, 56·45; H, 4·95; Cl, 9·3; 3OMe, 24·3%; *M*, 382·5. $C_{18}H_{21}O_7Cl$ requires C, 56·2; H, 5·45; Cl, 9·25; 3OMe, 24·2%; *M*, 384·5). Ultra-violet absorption max. in methanol: 330, 289, 236 mμ (log ε 3·73, 4·37, 4·42). It resembled griseofulvin in many respects, but was rather more soluble in cold chloroform or acetone; it gave a yellow colour in concentrated sulphuric acid and a brick-red precipitate with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, and slowly absorbed bromine in chloroform solution with evolution of hydrogen bromide on warming. With Girard's reagent P under standard conditions it gave a soluble complex from which there was recovered the starting material on acidification. Oxidation with chromic acid gave (II; R = Me), and with potassium permanganate gave (I). Alkaline hydrolysis gave 8-chloro-1 : 2 : 3 : 4-tetrahydro-3-keto-5 : 7-dimethoxy-1-methyldibenzofuran but no 7-chloro-4(or 6)-hydroxy-6(or 4)-methoxy-2′-methylgrisan-3 : 4′ : 6′-trione (cf. behavour of griseofulvin). Acid hydrolysis gave an *acid*, not identical with 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione, colourless prisms (from aqueous methanol), m. p. 253—255° (decomp.), $[\alpha]_D^{21}$ +237° (*c*, 0·096 as sodium salt in aqueous methanol) (Found: C, 55·3, 55·7; H, 4·9, 4·5; Cl, 10·2; OMe, 17·72. $C_{17}H_{17}O_7Cl$ requires C, 55·35; H, 4·6; Cl, 9·65; 2OMe, 16·8. $C_{17}H_{19}O_7Cl$ requires C, 55·05; H, 5·15; Cl, 9·6; 2OMe, 16·75%. Ultra-violet absorption max. in methanol: 330, 286 mμ (log ε, 3·87, 4·67), Oxidation of the acidic material with yellow mercuric oxide gave (XVIII).

We are indebted to Mr. H. A. Willis, Imperial Chemical Industries Limited, Plastics Division, for infra-red spectrographic facilities, to Professor H. Raistrick, Professor Sir Robert Robinson, and Professor A. R. Todd for interesting discussions on several aspects of this work, and to numerous colleagues who have made helpful suggestions.

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Imperial Chemical Industries Limited, Research Laboratories, Hexagon House, Manchester, 9. [*Received, February 22nd*, 1952.]

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763. *Griseofulvin. Part V.* Catalytic Reduction.*

By T. P. C. Mulholland.

Hydrogenation of griseofulvin may take three routes, *viz.*: (*a*) reduction of the double bond only, to give a product which on further hydrogenation undergoes reduction of the reactive keto-group and hydrogenolysis of the chlorine; (*b*) reduction to an alcohol and saturation of the ethylenic linking; or (*c*) reduction of the keto-group to an alcohol group which is hydrogenolysed to methylene, followed by reduction of the ethylenic linking. Hydrogenation of *iso*griseofulvin follows mainly route (*b*).

The present paper describes the reduction of griseofulvin (I) and *iso*griseofulvin (VI). The chemistry of the products is described in Part VI (following paper).

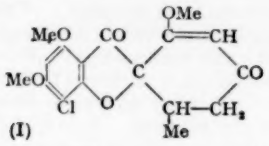
Griseofulvin.—In the first two experiments with palladised charcoal, reduction was slow, as described by Oxford, Raistrick, and Simonart (*Biochem. J.*, 1939, **33**, 240), giving dihydrogriseofulvin $C_{17}H_{19}O_6Cl$ (40%), and tetrahydrodeoxygriseofulvin $C_{17}H_{21}O_5Cl$ (26%), together with small amounts of two new products, $C_{17}H_{21}O_6Cl$ and $C_{17}H_{22}O_6$. In subsequent experiments, *ca.* 1·5 mols. of hydrogen were rapidly absorbed after which reduction became very slow. Interruption at the end of the rapid phase gave dihydrogriseofulvin (57%) as before. Only a small amount (3%) of tetrahydrodeoxygriseofulvin was formed and, instead, a third new compound $C_{17}H_{19}O_5Cl$ was obtained (26%). The reason for this is obscure. The change from slow to rapid initial reduction coincided with the use of fresh batches of materials in the catalyst.

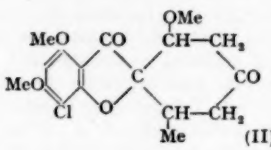
Reduction with a platinic oxide catalyst gave mainly the compound $C_{17}H_{21}O_6Cl$ and a small amount of tetrahydrodeoxygriseofulvin.

On further reduction with the palladised charcoal catalyst used for the second series of experiments, dihydrogriseofulvin gave only the chlorine-free compound, $C_{17}H_{22}O_6$.

* Part IV, preceding paper.

Only the starting material was isolated when the compound $C_{17}H_{21}O_6Cl$ was reduced, although the colour reaction with nitric acid suggested that some dechlorination may have occurred. The compound $C_{17}H_{19}O_5Cl$ gave tetrahydrodeoxygriseofulvin on reduction. Microhydrogenation of the latter with a platinic oxide catalyst did not reveal further ethylenic unsaturation.


(I)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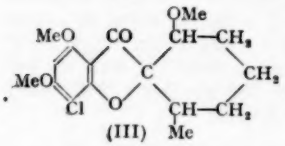
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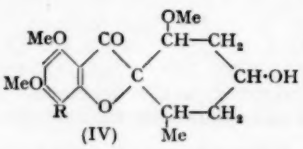
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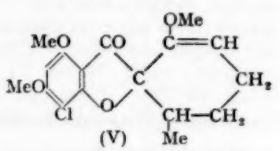

(V)

The ultra-violet absorption spectra showed that the main absorption bands, at 291 and 324 mμ, of griseofulvin were not affected by reduction, the carbonyl group conjugated with the aromatic ring remaining intact in the reduction products (Fig. 1). The presence of this carbonyl group in all the reduction products was confirmed by the infra-red spectra (Fig. 2); a band absorbing at *ca.* 1690—1700 cm.$^{-1}$ persisted in all the compounds except the compound $C_{17}H_{22}O_6$ in which the frequency was lowered to 1670 cm.$^{-1}$. In addition, the infra-red spectra showed that the compounds $C_{17}H_{22}O_6$ and $C_{17}H_{21}O_5Cl$ contained hydroxyl groups.

Oxidation of the latter substance gave dihydrogriseofulvin.

Clearly in dihydrogriseofulvin $C_{17}H_{19}O_6Cl$, tetrahydrodeoxygriseofulvin $C_{17}H_{21}O_5Cl$, and the compounds $C_{17}H_{21}O_6Cl$ and $C_{17}H_{22}O_6$, the ethylenic bond has been saturated. In addition, one of the carbonyl groups has been reduced to CH·OH in the last two compounds and to methylene in tetrahydrodeoxygriseofulvin. These compounds must therefore be represented by the structures tabulated below and derived from (I).

Formula	Name employed by Oxford *et al.* (*loc. cit.*)	New name	Structure
$C_{17}H_{19}O_6Cl$	Dihydrogriseofulvin	7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione	(II)
$C_{17}H_{21}O_5Cl$	Tetrahydrodeoxygriseofulvin	7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one	(III)
$C_{17}H_{21}O_6Cl$	—	7-Chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one	(IV; R = Cl)
$C_{17}H_{22}O_6$	—	4′-Hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one	(IV; R = H)

The presence of an αβ-unsaturated ketone system explains the formation of 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (III) and the failure to obtain this compound from the reduction of 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione (II), the ketone in the latter case being reduced to the chlorine-free alcohol (IV; R = H) but without subsequent hydrogenolysis. Similarly, 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = Cl) does not undergo hydrogenolysis on further reduction.

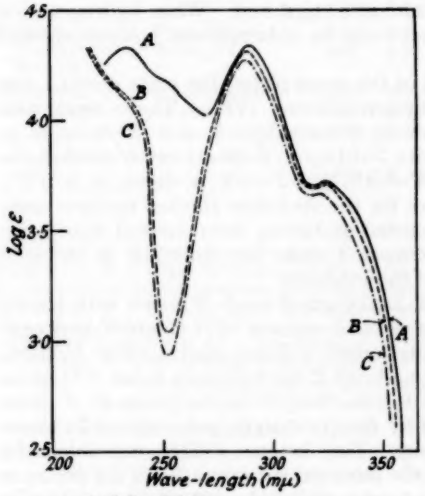
The formation of the compound $C_{17}H_{19}O_5Cl$ is of considerable interest because the analysis and properties indicate that, while the carbonyl group has undergone complete reduction to methylene, the ethylenic bond remains intact and is responsible for weak absorption in the infra-red at 1667 cm.$^{-1}$ (Fig. 2*e*). This compound is therefore 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one (V). As expected, it gives the fully saturated compound (III) on further reduction and is clearly the only precursor of the latter. Comparison of the yields in the first and the second series of experiments with palladium catalysts show that (V) is not formed at the expense of (II) and thus the course of the

reaction is the same in both series, but in the second the formation of (II) and (V) is much increased, while saturation of the latter remains a comparatively slow reaction.

The isolation of 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one appears not to have close analogies in the literature; although there are records of preferential reduction of the carbonyl group in unsaturated aldehydes, subsequent hydrogenolysis does not take place without simultaneous saturation of the ethylenic bond.

Griseofulvin (I) may thus be considered to undergo reduction in three ways: (i) Reduction of the double bond to give 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione

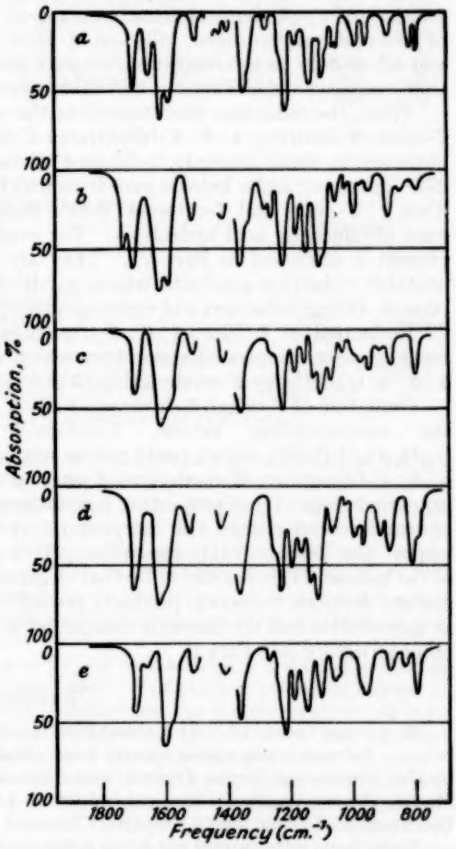
FIG. 1.



A, Griseofulvin.
B, Dihydrogriseofulvin.
C, Tetrahydrodeoxygriseofulvin.

FIG. 2.

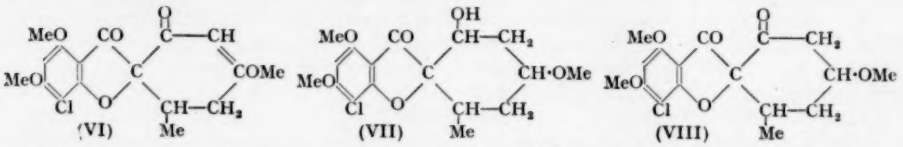
a, Griseofulvin (I); *b, dihydrogriseofulvin* (II); *c, 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one* (IV; R = Cl); *d, tetrahydrodeoxygriseofulvin* (III); *e, 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one* (V).



(II) which undergoes further reduction to 4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = H) and presumably 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = Cl). (ii) Reduction of the carbonyl to an alcohol group with saturation of the double bond, giving 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = Cl). (iii) Reduction of the carbonyl group followed by hydrogenolysis, giving 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one (V) and then by saturation of the double bond to give 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (III).

Thus all the theoretically possible products from reduction of the αβ-unsaturated ketone system in the hydroaromatic ring have been isolated, with the exception of the unsaturated alcohol; and there are indications that an unsaturated alcohol may be present

in the reduction products of 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione (VI) (see Part VI).



7-*Chloro*-4 : 6 : 4′-*trimethoxy*-6′-*methylgris*-3′-*en*-3 : 2′-*dione* (iso*Griseofulvin*) (VI).—In the presence of a palladium–charcoal catalyst, as with griseofulvin, there was a rapid absorption of two mols. of hydrogen, followed by slow uptake of a third mol. When hydrogenation was allowed to go to completion, no pure product could be obtained and analysis showed that extensive dechlorination had taken place.

When the reduction was stopped at the end of the rapid phase, the main product was 7-chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one (VII). There were also obtained, in small amounts, 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione, m. p. 275° (decomp.), and a ketonic gum from which both 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione and 7-chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione, m. p. 177°, were obtained by acid hydrolysis. The evidence for the structure allotted to these compounds is discussed in Part VI. They are regarded as having been derived from acid-unstable reduction products which partly decomposed under the influence of the acid present during reduction and chromatography of the products.

Reduction of 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione with Raney nickel gave a complex mixture from which only a small amount of 7-chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one and unchanged starting material were isolated.

Oxidation of 7-chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one (VII) gave the corresponding ketone, 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgrisan-3 : 2′-dione $C_{17}H_{19}O_6Cl$ (VIII), which could not be obtained by direct catalytic reduction of 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione. The ketone (VIII) resembles the isomeric ketone (II) in properties, but, although the infra-red spectrum shows the presence of two carbonyl groups, the compound does not form a dinitrophenylhydrazone. In this respect the ketone (VIII) resembles (VI) from which it is derived, while the reactivity of the ketone (II) is paralleled by that of griseofulvin (Part I). The existence of chemically distinct isomeric reduction products provides further evidence that the isomerism present in griseofulvin and the isomeric compound is positional and due to the 1 : 3-diketone enol ether structure (see Part I).

Experimental

M. p.s are corrected. The absorption spectra are given in Figs. 1 and 2 and the Tables below. Infra-red absorption spectra were obtained as described in Part I. Microanalyses are by Drs. Strauss and Weiler, Oxford (who determined some of the ultra-violet absorption spectra), Mr. W. Brown, Imperial Chemical Industries Limited, Butterwick Research Laboratories, and the Analytical Department, Imperial Chemical Industries Limited, Dyestuffs Division.

Reductions were carried out at room temperature and pressure.

In chromatography, except where stated, B.D.H. or Peter Spence's alumina (type H) was washed with 2N-nitric acid and with water, refluxed with methanol, and activated *in vacuo* for 3 hours at 250°, giving material of pH 4 and activity grade II (Brockmann and Schodder, *Ber.*, 1941, **74**, 73). Elution of the fluorescent bands was followed by intermittent inspection in ultra-violet light. The bands were colourless in daylight.

Griseofulvin. Reduction in Presence of Palladium.—(*a*) *Slow reduction.* Griseofulvin (4·0 g.) in ethyl acetate (400 ml.) was hydrogenated with a catalyst prepared from palladium chloride (2·5 g.), charcoal (8 g.), and water (150 ml.) as described by Oxford *et al.* (*loc. cit.*). Reduction was stopped after 13 hours (1·4 mols. of hydrogen absorbed). The crude product (3·5 g.) in carbon tetrachloride (150 ml.) was chromatographed on alumina (21·5 × 2·5 cm.) and the following bands collected. (i) Violet fluorescing band. Elution with ether–light petroleum (1 : 1) gave 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (III) (1·0 g., 26%), colourless

needles (from ethanol), m. p. 181°, $[\alpha]_D^{22}$ −34° (*c.* 1·0 in acetone) (Found: C, 59·9; H, 6·1; Cl, 10·4; OMe, 26·6. Calc. for $C_{17}H_{21}O_6Cl$: C, 59·9; H, 6·1; Cl, 10·4; 3OMe, 27·3%). It was saturated to neutral permanganate, and microhydrogenation in acetic acid with Adams's catalyst did not reveal further ethylenic unsaturation.

Ultra-violet absorption spectra (in methanol).

Compound	$\lambda_{max.}$	log ε	Compound	$\lambda_{max.}$	log ε
7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (III)	322	3·68	7-Chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = Cl)	323	3·67
	287	4·28		287	4·29
	~234	4·10		~230	4·11
7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione (II)	323	3·70	7-Chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one (VII)	322	3·70
	288	4·31		289	4·33
	~234	4·10		~240	4·07
4′-Hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = H)	~314	3·69	7-Chloro-4 : 6 : 4′-trimethoxy-6′-methylgrisan-3 : 2′-dione (VIII)	323	3·73
	282	4·31		289	4·20
				~242	3·99
7-Chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one (V)	325	3·71			
	288	4·32			
	236	4·16			

Infra-red absorption spectra.

Compound	Frequency assignments (cm.$^{-1}$) CO	OH
7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (III)	1700	—
7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione (II)	1725, 1700	—
4′-Hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = H)	1670	3448
7-Chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one (V)	1702	—
7-Chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = Cl)	1695	3425
7-Chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one (VII)	1690	3450
7-Chloro-4 : 6 : 4′-trimethoxy-6′-methylgrisan-3 : 2′-dione (VIII)	1730, 1693	—

Of the above, only (V) had ethylenic C=C absorption [at 1667 (weak)].

(ii) Violet fluorescing band. Elution with ether + 1% of methanol gave 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione (II) (1·6 g., 40%), colourless needles (from ethanol), m. p. 198°, $[\alpha]_D^{22}$ −20° (*c.* 1·0 in acetone). Some specimens from subsequent experiments (see below) had m. p. 206—208° (Found: C, 57·4; H, 5·3; Cl, 9·55; OMe, 25·3. Calc. for $C_{17}H_{19}O_6Cl$: C, 57·5; H, 5·4; Cl, 10·0; 2OMe, 26·2%). The *oxime* crystallised from dilute ethanol in plates, m. p. 255—256° (decomp.) (Found: C, 55·2; H, 5·5; N, 3·8. $C_{17}H_{20}O_6NCl$ requires C, 55·2; H, 5·45; N, 3·8%). As reported by Oxford *et al.* (*loc. cit.*), the dione (II) gave a precipitate with Brady's reagent but no satisfactory analyses could be obtained for this derivative.

(iii) Streaky green band. Elution with ether + 3% of methanol gave a solid crystallising from ethanol in colourless needles (0·07 g.), m. p. 180—190°. The product contained solvent of crystallisation, lost on heating. It was rechromatographed and the middle fraction (58 mg.) crystallised from benzene in prisms, m. p. 185—188°, identical (mixed m. p. and infra-red spectrum) with 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (see below).

(iv) Narrow purple fluorescing band. Elution with ether + 3% of methanol gave *4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one* (IV; R = H), colourless needles (from ethanol), m. p. 222—223°, $[\alpha]_D^{22}$ −10° (*c*, 0·5 in acetone) (Found: C, 62·9; H, 6·7; Cl, nil; OMe, 28·0. $C_{17}H_{22}O_6$ requires C, 63·3; H, 6·9; 3OMe, 28·8%). It did not react with neutral permanganate or Brady's reagent and, unlike the chlorine-containing derivatives of griseofulvin, gave an intense violet colour with concentrated nitric acid.

(*b*) *Rapid reduction.* Griseofulvin (2·0 g.) in ethyl acetate (200 ml.) was reduced as before with a catalyst prepared from a fresh batch of palladium chloride (1·0 g.), water (90 ml.), and charcoal (4·0 g.). Hydrogen was absorbed rapidly during 10 minutes (*ca.* 1·6 mols. of hydrogen) and then more slowly. After 15 minutes (1·7 mols. of hydrogen) the reaction was stopped. The crude product, in benzene (70 ml.), was chromatographed on alumina (21·5 × 2·5 cm.). The first two violet bands were eluted as in the previous experiment. Recovery gave colourless solids. The first (0·75 g.), on fractional crystallisation from ethanol and benzene–light petroleum, gave 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one, m. p. 180° (0·06 g., 3%) and the less soluble *7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one* (V) (0·5 g., 26%) which crystallised from ethanol or from benzene-light petroleum in long slender colourless needles, m. p. 194—195°,

$[\alpha]_D^{20}$ +155° (*c*, 1·0 in acetone) [Found: C, 60·2, 60·4; H, 5·65, 5·7; Cl, 10·4, 10·7; OMe, 26·2; *M* (Rast), 305. $C_{17}H_{19}O_6Cl$ requires C, 60·3; H, 5·65; Cl, 10·5; 3OMe, 27·5%; *M*, 358]. This compound did not react with Brady's reagent. Although it did not react with bromine in chloroform in the cold, and was attacked very slowly by neutral permanganate, the presence of unsaturation was shown by catalytic reduction to 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (see below).

The second solid was 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione (1·15 g., 57%). Rechromatography, followed by crystallisation from ethanol, gave colourless needles, m. p. 202—203° (0·9 g.).

A similar result was obtained in all subsequent experiments, the ratio of 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione to 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one approximating to 5 : 2. The purest specimens of the former, m. p. 206—208°, were obtained when the chromatographic separation was carried out as rapidly as possible and with the minimum of exposure to ultra-violet light.

Griseofulvin. Reduction in Presence of Platinum Oxide.—(a) *Partial reduction.* Hydrogenation of griseofulvin (3·34 g.) in glacial acetic acid (300 ml.) in the presence of Adams's catalyst (500 mg.) was stopped after hydrogen (1·3 mols.) had been absorbed in 18 minutes. The crude solid (3·55 g.) obtained on removal of the catalyst and solvent was chromatographed in benzene on alumina (19·6 × 2·5 cm.) and the following bands collected. (i) Violet fluorescing band eluted with benzene. Recovery gave a solid (315 mg.), which, after crystallising from benzene–light petroleum, had m. p. 174—175°, not depressed by mixture with 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one.

(ii–iv) A blue band followed by an interband and a violet band were eluted with benzene followed by ether + 1% of methanol and gave intractable products (798 mg.).

(v) Violet band. Elution with ether + 2% of methanol gave unchanged griseofulvin (1·33 g.), m. p. and mixed m. p. 217—219°.

(vi) The remaining band was cut from the extruded column and extracted with methanol. Recovery gave *7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one* (IV; R = Cl)) (174 mg.) which crystallised from benzene in prisms, m. p. 197—198°, containing solvent of crystallisation, lost on heating, $[\alpha]_D^{22}$ −17° (*c*, 1·0 in acetone) (Found: C, 57·5; H, 5·9; Cl, 9·6; OMe, 24·1. $C_{17}H_{21}O_6Cl$ requires C, 57·2; H, 5·9; Cl, 9·9; 3 OMe, 26·1%). This compound was identical (mixed m. p. and infra-red spectrum) with impure material obtained by reduction with palladium. It did not react with Brady's reagent, Fearon and Mitchell's reagent, or ferric chloride, or give an alkali xanthate. It was saturated to neutral permanganate.

The *monoacetyl* derivative (acetic anhydride in pyridine at 34° for 4 days) crystallised from ethanol in colourless crystals, m. p. 208—209° (Found: C, 56·6; H, 5·75. $C_{19}H_{23}O_7Cl$ requires C. 57·2; H, 5·8%).

(b) *Complete reduction.* Hydrogenation of griseofulvin (1·43 g.) in acetic acid (100 ml.) with the catalyst recovered from (*a*) was allowed to go to completion (3 mols. in 1 hour). The product (1·55 g.) in benzene (25 ml.) was chromatographed on alumina (pH 8) (14 × 2·0 cm.). Development with benzene gave a blue fluorescing band of general absorption and an upper fluorescing band. The lower band was eluted with benzene, giving a solid (674 mg.) which on repeated crystallisation from benzene and aqueous methanol gave a little 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one. The same substance (222 mg.) was obtained by elution of the upper band with benzene + 1% of methanol. The solid (630 mg.), recovered from the crystallisation mother-liquors, was rechromatographed in the same way on alumina (15·5 × 2·0 cm.) and eluted with benzene. The lower band (violet fluorescence) gave 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (204 mg.), identified by analysis and infra-red spectrum. The upper violet fluorescing band gave the alcohol (IV; R = Cl) (113 mg.), m. p. 194—196°. A colourless interband gave intractable material (250 mg.).

7-Chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one.—(i) *Oxidation.* The compound (120 mg.) in acetic acid (2·5 ml.) was treated in portions with chromic oxide (234 mg.) in acetic acid (0·9 ml.) and water (0·4 ml.). After each addition the mixture was warmed until the chromic oxide was consumed and when addition was complete the mixture was heated under reflux (1 minute), cooled, diluted with water (25 ml.), and extracted with benzene. The extract, after being washed with water and evaporated, gave a gum which solidified on trituration with ether. After being washed with ether, the solid (5 mg.) crystallised from benzene–light petroleum in microcrystalline clumps, m. p. 203—205°, identified as 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione by mixed m. p. and infra-red spectrum.

(ii) *Reduction.* The compound (343 mg.) in ethyl acetate (30 ml.) was hydrogenated with a

catalyst prepared from palladium chloride (0·2 g.), water (12 ml.), and charcoal (0·75 g.). Hydrogen (*ca.* 0·9 mol.) was absorbed in 2 days. Chromatography of the product yielded only intractable fractions in addition to unchanged starting material (0·22 g.), m. p. and mixed m. p., 190—193°, after crystallisation from benzene. Material from the mother-liquor gave a blue colour with concentrated nitric acid indicating that some dechlorination had occurred (see Part VII).

Reductive Dechlorination of 7-*Chloro*-4 : 6 : 6′-*trimethoxy*-2′-*methylgrisan*-3 : 4′-*dione*.—The compound (0·5 g.) in ethyl acetate (40 ml.) was hydrogenated in the presence of a catalyst prepared from palladium chloride (0·5 g.), water (35 ml.), and charcoal (1·8 g.). Absorption proceeded slowly and was not accelerated by addition after 1 hour of 3N-hydrochloric acid (1 ml.). After 19 hours (1·5 mols. absorbed), the crude product was obtained in the usual way and chromatographed in benzene (10 ml.) on alumina (15·5 × 2·0 cm.); giving (*a*) an ill-defined violet fluorescing band which gave a few mg. of a colourless solid, m.p. 142—144°, (*b*) a broad violet fluorescing band, from which ether + 2% of methanol gave starting material (90 mg.), m. p. and mixed m. p. after crystallisation, 198°, (*c*) an interband with little fluorescence giving a solid (85 mg.), which after crystallisation from benzene–light petroleum had m. p. 205—210°, not depressed on admixture with fraction (*d*), and (*d*) a dull violet band, from which ether + 10% of methanol gave 4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (100 mg.), colourless plates (from benzene), m. p. 220—222° (Found: C, 63·3; H, 6·8; Cl, nil. Calc. for $C_{17}H_{22}O_6$: C, 63·3; H, 6·9%).

Reduction of 7-*Chloro*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3-*one*.—The compound (358 mg.) in ethyl acetate (30 ml.) was hydrogenated in the presence of a catalyst prepared from palladium chloride (0·2 g.), water (12 ml.), and charcoal (0·75). After 3 hours (1·0 mol. absorbed) the crude product was isolated and crystallised from ethanol, giving a solid A (0·12 g.) from which unchanged starting material, m. p. and mixed m. p. 192—193°, was recovered by repeated crystallisation from benzene–light petroleum. Evaporation of the ethanolic mother-liquor from (A) gave a solid (0·13 g.) which, after crystallisation from benzene–light petroleum and from ethanol, was obtained with m. p. 181° and identified as 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one by mixed m. p., infra-red spectrum, and analysis.

Reduction of 7-*Chloro*-4 : 6 : 4′-*trimethoxy*-6′-*methylgris*-3′-*en*-3 : 2′-*dione* (VI).—A solution of the compound (2·0 g.) in ethyl acetate (200 ml.) was reduced in the presence of a catalyst prepared from palladium chloride (1·0 g.), water (120 ml.), and charcoal (4·0 g.). Reduction was stopped after 20 minutes (2·0 mols. absorbed), when the rate of the reduction had become very slow. The crude product in benzene (100 ml.) was chromatographed on alumina (21 × 3·0 cm.). Elution with ether + 1% of methanol gave a violet band with a bright lower fringe. Elution of the violet fringe gave a colourless solid, m. p. 240—°260 (14 mg.), which was not ketonic to Brady's reagent. This fraction was rechromatographed and from the middle fraction 3 mg. of colourless material were obtained, having m. p. 268—270° (decomp.) and identified by mixed m. p. and infra-red spectrum as 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione, m. p. 275—277° (decomp.), obtained by a different method (Part VI). A violet band gave a gum (*ca.* 0·4 g.) separated by trituration with ether into two intractable fractions (A, 60 mg., m. p. 50—60°; and B, a gum; each of these fractions was submitted to acid hydrolysis as described below). A large band, eluted with ether + 5% of methanol, gave a gum (1·0 g.) which was washed with ether and crystallised from ethanol as colourless needles, m. p. 228—230°, $[\alpha]_D^{19}$ −29° (*c.* 0·85 in acetone) of 7-*chloro*-6′-*hydroxy*-4 : 6 : 4′-*trimethoxy*-2′-*methylgrisan*-3-*one* (VII) (Found: C. 57·5; H, 6·0; Cl, 10·3; OMe, 26·2. $C_{17}H_{21}O_6Cl$ requires C, 57·2; H, 5·9; Cl, 9·9; 3OMe, 26·1%). The properties closely resembled those of 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one.

Hydrolysis of fractions A and B. A. The solid (0·12 g.) in acetic acid (2·0 ml.) and water (0·4 ml.) was heated under reflux for 2 hours. The gum obtained by evaporation to dryness was chromatographed on alumina (6 × 1·0 cm.) from its benzene solution (3 ml.). The following fractions were eluted with ether + 1% of methanol: (*a*) narrow band with violet fluorescence giving a trace of solid, m. p. 220—230°; (*b*) a band with faint fluorescence yielding a solid (6 mg.) which crystallised from ethanol in colourless needles, m. p. 262—266° (decomp.), not depressed on admixture with 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione, m. p. 274° (decomp.) (see Part VI); and (*c*) a diffuse violet fluorescing band which gave a trace of gum.

B. The gum, in acetic acid (5 ml.) and concentrated hydrochloric acid (0·5 ml.), was heated under reflux (5 minutes) and diluted with water. The precipitated gummy solid was chromatographed in benzene on alumina (12·5 × 1·0 cm.), and the following fractions collected: (a) a violet fluorescing band which, when eluted with ether, gave a solid (9 mg.), m. p. 170—172°;

(*b*) a band, eluted with ether, giving a solid (10 mg.), m. p. 170—174°; and (*c*) a violet fluorescing band eluted with ether + 1% of methanol, giving a solid (2 mg.), m. p. 263—270° after softening from 220°. It was non-ketonic to Brady's reagent and probably was impure 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-ene-3 : 2′-dione. The combined solids from (*a*) and (*b*) crystallised from benzene–light petroleum in colourless microcrystalline clumps, m. p. 173—174°, identical (mixed m. p. and infra-red spectrum) with 7-chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione, described in Part VI.

When hydrogenation of 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione was conducted as in the previous experiment for 2 days, *ca.* 3 mols. of hydrogen were absorbed but the product, m. p. 181—182°, obtained by chromatography and subsequent crystallisation gave a blue colour with concentrated nitric acid indicating that dechlorination had occurred (see above). Analysis confirmed the loss of chlorine (Found: Cl, 3·7. Calc. for $C_{17}H_{21}O_5Cl$: Cl, 9·9%).

Reduction of this compound in ethanol with Raney nickel resulted in the uptake of *ca.* 3 mols. of hydrogen in 2 hours. Chromatography showed the product to be very complex, and the only compounds identified were a little unchanged starting material and 7-chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one. Addition of chloroform (2%) inhibited reduction.

Oxidation of 7-Chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one.—The compound (400 mg.), dissolved in warm acetic acid (8 ml.), was oxidised by dropwise addition of chromic acid (760 mg.) in acetic acid (3 ml.) and water (1·2 ml.). The procedure previously described for the oxidation of 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one was followed, giving a gum. When scratched with ether (3 ml.), *7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgrisan-3 : 2′-dione* (VIII) (89 mg.) crystallised. After being washed with ether, it crystallised from ethanol in colourless plates, m. p. 177—178° (Found: C, 57·4; H, 5·6; Cl, 10·4; OMe, 25·9. $C_{17}H_{19}O_6Cl$ requires C, 57·5; H, 5·4; Cl, 10·0; 3OMe, 26·2%). The compound did not react with Brady's reagent and was not attacked by neutral permanganate. It was insoluble in cold 3N-sodium hydroxide but decomposed when warmed, giving a yellow solution.

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The Frythe, Welwyn, Herts. [*Received, February 22nd,* 1952.]

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764. *Griseofulvin. Part VI.* Chemistry of the Reduction Products.*

By T. P. C. Mulholland.

The chemistry of the reduction products of griseofulvin and the isomeric 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione (*iso*griseofulvin) is described. The reactions are consistent with the formulæ proposed for these compounds in Part V and provide conclusive proof for the orientation of the two isomers. The compound $C_{16}H_{19}O_5Cl$ (product B) obtained by catalytic reduction of 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione (griseofulvic acid) (Part I, *J.*, 1952, 3949) is shown to be 7-chloro-6′-hydroxy-4 : 6-dimethoxy-2′-methylgrisan-3-one (XVIII).

In the preceding paper it was shown that catalytic reduction of griseofulvin (I) gave five products, *viz.*: (II), (III; R′ = Cl), (III; R′ = H), (IV), and (V). On the other hand, reduction of *iso*griseofulvin (VI) gave mainly (VII), isomeric with (III; R′ = Cl). The corresponding ketone (VIII), isomeric with (IV), was prepared by oxidation of (VII). In the present paper, an account is given of the chemistry of these products. The relations between the more important compounds discussed are outlined in the annexed scheme.

The stability of (V) to acid and alkaline hydrolysis (Oxford *et al.*, *loc. cit.*) was confirmed. The reduction product (III; R′ = Cl) showed a similar stability. The compounds (III; R′ = H) and (VII) were not attacked by aqueous 3N-sodium hydroxide. These results,

* Part V, preceding paper.

although incompatible with the ester structure proposed for griseofulvin by Oxford *et al.* (*loc. cit.*), are consistent with the structures (I) and (VI) proposed in Part IV (*J.*, 1952, 3977) for griseofulvin and the isomeric *iso*griseofulvin respectively since these show the reduction products as saturated ethers.

Now, if griseofulvin and *iso*griseofulvin are respectively (I) and (VI), and not *vice versa*, the corresponding dihydro-derivatives are (IV) and (VIII). Then (IV), as a saturated ether, should resist alkaline hydrolysis, like the corresponding alcohol (III; R′ = Cl). On the other hand, (VIII), as a 1 : 3-diketone, should be susceptible to alkaline hydrolysis. It should thus be possible to test the structural assignments.

As expected, the dihydro-derivative of (VI) was unstable to alkali, but the small amount of material available prevented the characterisation of the products. However, the dihydro-derivative of (I) was also unstable to alkali, and hydrolysis in an inert atmosphere gave 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (IX), an intractable neutral fraction, and a phenolic fraction. Examination of the infra-red spectrum of the phenolic fraction by Mr. T. A. Kletz, Imperial Chemical Industries Limited, Billingham Division, disclosed that it consisted of *m*-cresol containing about 10% of 2 : 5-dihydroxytoluene. A study of the behaviour of (IV) towards acid hydrolysis provided an explanation of this unexpected cleavage.

In dilute ethanolic sulphuric acid, (IV) lost the elements of methanol, affording a neutral unsaturated dimethoxy-compound, $C_{16}H_{15}O_5Cl$ (X), which contained a chemically reactive carbonyl group. Infra-red analysis showed the presence of two carbonyl groups. As in griseofulvin and the reduction products, the coumaranone-carbonyl group was still present, absorbing at 1697 cm.$^{-1}$ The second carbonyl group absorbed at 1670 cm.$^{-1}$, compared with 1725 cm.$^{-1}$ in (IV) and 1650 cm.$^{-1}$ in griseofulvin. The lowered frequency in the ketone (X) and in griseofulvin is consistent with the presence of an αβ-unsaturated carbonyl group in both compounds. The ketone (X) is thus the vinylogue of a 1 : 3-diketone and as expected is broken down by alkali to the acid (IX), an unresolved neutral fraction, and a phenolic fraction similar to the phenolic fraction obtained by alkaline hydrolysis of (IV). The formation of the same products from (IV) and (X) suggests that the latter is an intermediate in this reaction. Easy degradation of (IV) to the acid (IX) and *m*-cresol by alkali is therefore to be expected. The formation of 2 : 5-dihydroxytoluene is probably due to the presence of enough oxygen to cause part of the intermediate (XI) to undergo oxidative degradation instead of dehydration to *m*-cresol.

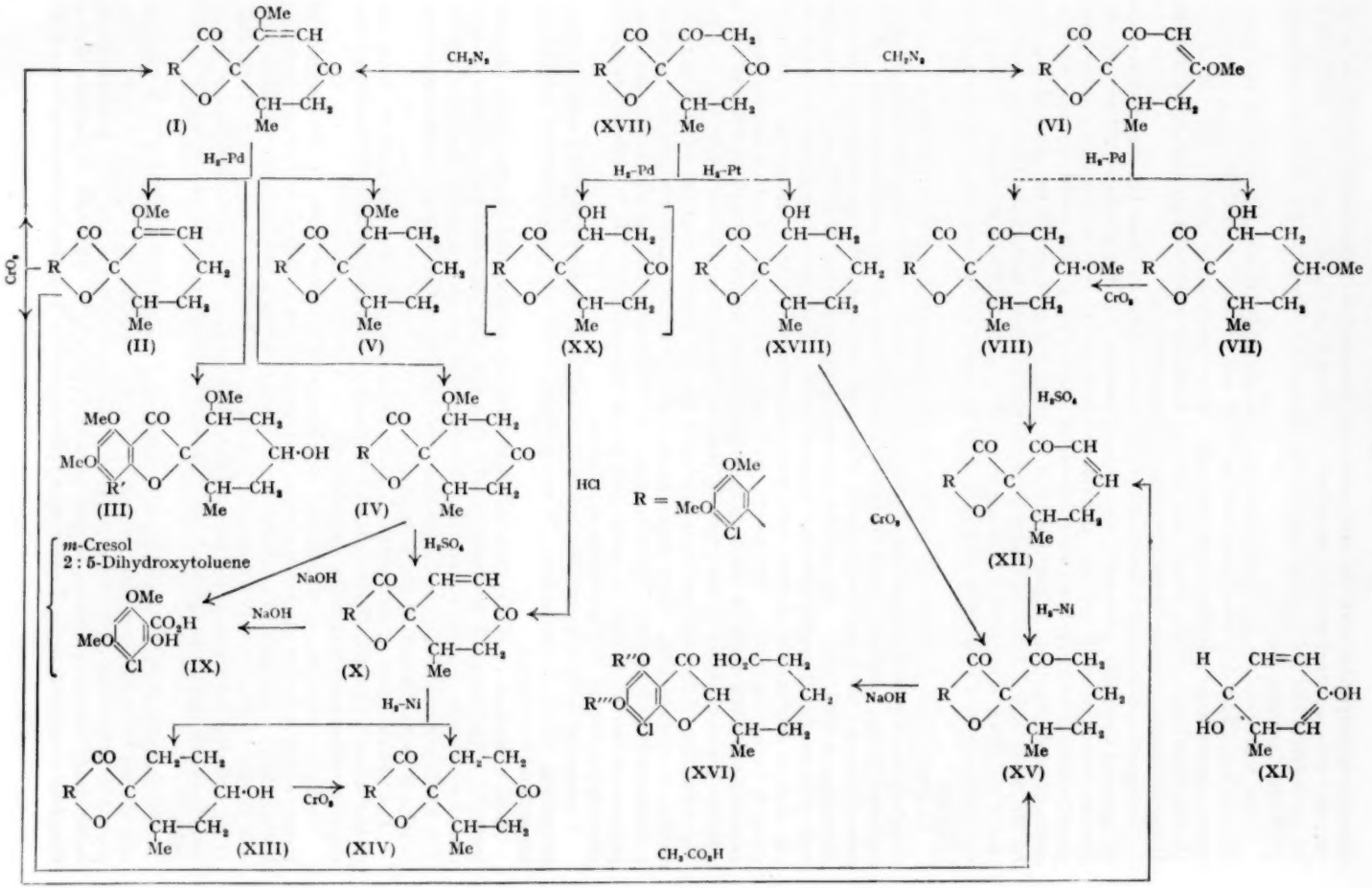
During acid hydrolysis of (IV), traces of a saturated ketone $C_{18}H_{21}O_6Cl$ were isolated, resembling (IV) in its properties. It was probably formed by replacement of a methoxyl substituent by ethoxyl.

Acid hydrolysis of (VIII) gave an alkali-unstable unsaturated ketone (XII), isomeric with (X). The infra-red spectrum showed that this also contained two carbonyl groups, one of which was αβ-unsaturated, but the ketone did not form a dinitrophenylhydrazone. The formation of (XII) is considered to involve the loss of the elements of methanol from (VIII), as in the formation of (X) from (IV).

The desired proof of structures (I) and (VI) respectively was obtained by reduction of the ketones (X) and (XII) to the corresponding saturated ketones which showed the expected differences in stability to hydrolysis.

Catalytic reduction of the ketone (X), derived from griseofulvin, in the presence of Raney nickel gave the saturated alcohol (XIII) which was oxidised to the corresponding ketone (XIV); the latter was obtained also directly when a small amount of chloroform was present during the reduction (cf. Cornubert and Phélisse, *Compt. rend.*, 1948, **227**, 1131). Similar reduction of the ketone (XII), derived from (VI), in the presence of Raney nickel gave an intractable product but addition of chloroform led to the saturated ketone (XV).

The compound (XIV) is neither a 1 : 3-diketone nor the vinylogue of a 1 : 3-diketone and should be stable to alkali; but (XV) is a 1 : 3-diketone and should be split. This proved to be the case, (XIV) being stable to 3N-sodium hydroxide, and (XV) breaking down under much milder conditions to give an acid $C_{15}H_{17}O_6Cl$. This acid is phenolic and is therefore considered to be 7-chloro-4(or 6)-hydroxy-6(or 4)-methoxycoumaran-3-one-2-5′-


(I)
(XVII)
(VI)
(II)
(V)
(XX)
(XVIII)
(VIII)
(VII)
(III)
(IV)
(XII)
(IX)
(X)
(XVI)
(XV)
(XI)
(XIII)
(XIV)
R = MeO Cl
m-Cresol
2 : 5-Dihydroxytoluene

hexanoic acid (XVI; R′ = H, R″ = Me or *vice versa*). The ready hydrolysis of an aryl methyl ether, though unusual, takes place with a number of griseofulvin derivatives (see Parts I and II).

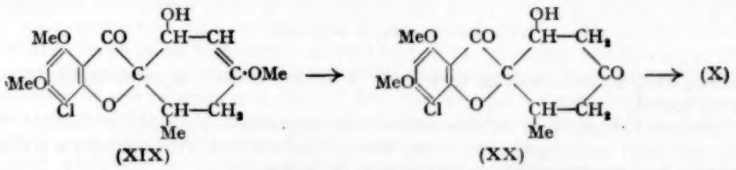
7-Chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′-dione (XV) is identical with the ketone obtained by the chromic acid oxidation of the compound B, $C_{16}H_{19}O_5Cl$, one of the reduction products of 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione (griseofulvic acid) (XVII) (see Part I). Therefore the product B is (XVIII), and not (XIII).

Whereas griseofulvin and the ketones (X) and (XIV) react readily with carbonyl reagents, 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione and the ketones (XII) and (XV) derived from it do not, probably owing to steric hindrance. It may also be noted that the specific rotations of 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione and of 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione are considerably lower than those of griseofulvin and 7-chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione respectively.

The chemistry of the compound $C_{17}H_{19}O_5Cl$ (II), obtained by reduction of griseofulvin, is consistent with the structure proposed in Part V. As an enol ether it is stable to aqueous alkali, but is converted into 7-chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′-dione (XV) by dilute acetic acid. If no rearrangement has taken place, the compound $C_{17}H_{19}O_5Cl$ must be 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one (II). That this is so was shown by oxidation of (II) to griseofulvin by chromic acid. A second oxidation product is 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-ene-3 : 2′-dione (XII) and the probable sequence of reactions leading to the formation of this compound is discussed below.

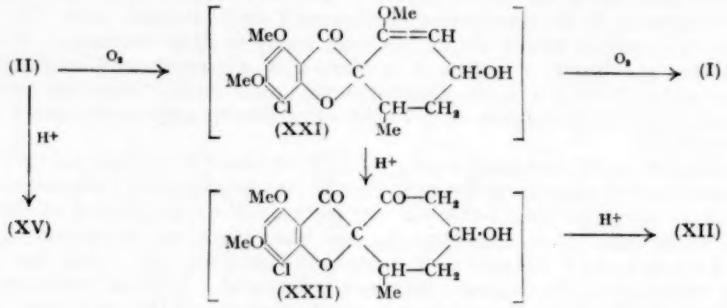
Although (II) is stable to aqueous sodium hydroxide in concentrations up to 25%, 20% alcoholic potassium hydroxide brings about exchange of ethoxyl for methoxyl, leaving the main skeleton of the molecule unchanged. The crude product is a mixture of at least two and probably three compounds, of which one is a diethoxy- and another a monoethoxy-compound, whilst the third is probably an isomeric monoethoxy-compound. The infrared spectra of all those compounds are almost identical with that of 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one. Sodium ethoxide has a similar effect on other compounds of the griseofulvin series (see Part IV).

Two points call for further explanation. (i) It has been shown in Part V that both 7-chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione (X) and 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione (XII) are obtained on reduction of 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione (VI). Since (XII) can also be obtained by the action of acid on 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgrisan-3 : 2′-dione (VIII), it is assumed that some of the latter compound was formed during the reduction but was decomposed by the acid present during chromatography of the product. The formation of (X) is more difficult to explain. It is possible that the unsaturated alcohol (XIX) is formed, which, in the presence of acid, gives 7-chloro-6′-hydroxy-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (XX), whence (X) would result by loss of water. This mechanism receives some support from the partial reduction of 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione (XVII) with a palladium catalyst to a gum from which 7-chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione was obtained by hydrolysis. Similarly, Auterinen (*Suomen Kemi.*, 1937, **10**, *B*, 22; *Chem. Abs.*, 1938, **32**, 509) has shown that the dimedone reduction product 3-hydroxy-5 : 5-dimethyl*cyclo*hexanone is unstable and readily loses water to give 5 : 5-dimethyl*cyclo*hex-2-enone.



(ii) Oxidation of (II) to griseofulvin and 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione (XII) (see above) is most readily explained by a similar series of reactions.

The issue is complicated by the possibility of simultaneous hydrolysis. However, hydrolysis of (II) without oxidation gives 7-chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′-dione (XV); this cannot be an intermediate in the formation of (XII) as it does not yield (XII) when oxidised under identical conditions. It is possible that the methylene group, activated by the adjacent double bond, is oxidised, giving the unsaturated alcohol (XXI) which (*a*) gives griseofulvin (I) on further oxidation, or (*b*), as an enol ether, is hydrolysed by acid to (XXII), which yields (XII) by dehydration under the influence of acid.



7-Chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione (XII) was first isolated by Dr. M. A. T. Rogers by reduction of griseofulvin with aluminium *iso*propoxide. The results were not always reproducible and in some experiments only unchanged starting material was recovered. The mode of formation of (XII) in this reaction remains obscure, but it is likely that the unsaturated alcohol (XXI) figures as an intermediate also in this reaction.

Exeprimental

M. p.s are corrected. Absorption spectra are collected in Tables 1 and 2. Infra-red spectra were obtained as described in Part I. Microanalyses are by Drs. Strauss and Weiler, Oxford, who determined the ultra-violet spectra, and Mr. W. Brown, Imperial Chemical Industries Limited, Butterwick Research Laboratories. For chromatography, see Part V. Almost all the compounds gave rise to bands of blue to violet fluorescence.

Attempted Hydrolysis.—(i) *7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one* (V). Only starting material was recovered after being heated under reflux with N-ethanolic sulphuric

Table 1.

Compound	Frequency assignments (cm.⁻¹) CO	C=C ethylenic	OH
7-Chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione (X) ...	1697, 1760	—	—
7-Chloro-4′-hydroxy-4 : 6-dimethoxy-2′-methylgrisan-3-one (XIII)	1690	—	3346
7-Chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (XIV)	1713, 1703	—	—
7-Chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′-dione (XV)	1728, 1700	—	—
7-Chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione (XII)...	1690, 1667	—	—
7-Chloro-4(or 6)-hydroxy-6(or 4)-methoxycoumaran-3-one-2-(5′-hexanoic acid (XVI)	1702, 1670	—	2660b
Compound A	1708	1672w	—
Compound B	1707	1670w	—
Compound C	1707	1670w	—

w = weak, b = broad.

acid (6 hours), 24% aqueous sodium hydroxide (3 hours), or 20% aqueous alcoholic potassium hydroxide (3 hours).

(ii) *7-Chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one* (III; R′ = Cl). The compound was recovered unchanged after being heated under reflux with aqueous N-sodium hydroxide (3 hours) or with ethanolic N-sulphuric acid (6 hours).

(iii) *4′-Hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one* (III; R = H). This was insoluble in boiling 3N-sodium hydroxide.

TABLE 2. *Ultra-violet absorption spectra (in methanol).*

Compound	$\lambda_{max.}$ (mμ)	log ε	Compound	$\lambda_{max.}$ (mμ)	log ε
7-Chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one (XIII)	324	3·71	7-Chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione (XII)	326	3·69
	287	4·37		290	4·27
	~238	4·08		228	4·40
7-Chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (XIV)	324	3·71	Compound A	327	3·74
	288	4·37		289	4·39
	~238	4·08		~228	4·33
	213	4·35			
			7-Chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione (X)	326	3·70
7-Chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′-dione (XV)	~326	3·69		291	4·32
	291	4·28		220	4·35
	~239	3·98			
	216	4·24			

7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione (IV).—(a) *Alkaline hydrolysis.* A solution of the compound (200 mg.) in sodium hydroxide (15 ml.; N) and ethanol (10 ml.) was heated under reflux in nitrogen for 3 hours. The tar obtained by concentration and cooling was collected (43 mg.; A). After extraction with benzene, the filtrate was saturated with carbon dioxide and diluted. A phenolic gum (*ca.* 10 mg.; B) was recovered in ether. Acidification of the aqueous layer with hydrochloric acid caused separation of fraction C (75 mg.).

The neutral fraction A, m. p. 115—200°, contained chlorine but was intractable.

Distillation of the fraction B *in vacuo* gave an oil with a strong phenolic smell. It gave a blue colour with Gibbs' reagent and was shown by Mr. T. A. Kletz, Imperial Chemical Industries Limited, Billingham Division, using a reflecting microscope attached to an infra-red spectrometer, to consist of *m*-cresol mixed with about 10% of 2 : 5-dihydroxytoluene.

Fraction C, crystallised from ethyl acetate or ethyl methyl ketone in colourless needles, m. p. 220—221° (decomp.), identified as 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid by mixed m. p., infra-red absorption spectrum, and *X*-ray powder diagram (Found: C, 46·8; H, 4·05; Cl, 14.95. Calc. for $C_9H_9O_5Cl$: C, 46·45; H, 3·9; Cl, 15·25%).

(b) *Acidic hydrolysis.* The compound (5·3 g.) was heated under reflux with sulphuric acid (635 ml.; 2N) and ethanol (480 ml.) for 6 hours. The solid (3·0 g.), obtained by concentration *in vacuo* and filtration, was chromatographed in benzene (100 ml.) on alumina (27 × 3 cm.). The following fractions were eluted with ether + 1% of methanol: (i) A band with violet fluorescence. The solid (?) *ethoxy-ketone* (43 mg.) remaining after recovery and washing with ether crystallised from benzene–light petroleum in colourless crystals, m. p. 156—157° (Found: C, 58·3; H, 5·6; Cl, 9·6. $C_{15}H_{21}O_6Cl$ requires C, 58·6; H, 5·7; Cl, 9·6%). It gave a precipitate with Brady's reagent on warming, was saturated to neutral permanganate, and, although insoluble in cold 3N-sodium hydroxide, partly dissolved on warming to give a yellow solution. (ii) A dark band, giving *7-chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione* (X) (2·5 g.), which crystallised from ethanol in colourless needles, m. p. 177—178°, $[\alpha]_D^{21}$ +442° (*c.* 0·96 in acetone) (Found: C, 59·6; H, 4·85; Cl, 10·65; OMe, 19·5. $C_{16}H_{15}O_5Cl$ requires C, 59·5; H, 4·7; Cl, 11·0; 2OMe, 19·2%). The *dinitrophenylhydrazone* crystallised from light petroleum–acetic acid in orange yellow needles, m. p. 282—283° (decomp.) (Found: N, 11·0. $C_{22}H_{19}O_8N_4Cl$ requires N, 11·15%). The ketone was unsaturated to neutral permanganate and bromine water, but did not reduce Fehling's solution or give a colour with ferric chloride. It was insoluble in cold 3N-sodium hydroxide but partly dissolved when heated giving a yellow colour, discharged on acidification.

Alkaline Hydrolysis of 7-Chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione.—The ketone (230 mg.), sodium hydroxide (50 ml.; N), and enough methanol to give a homogeneous solution were heated under reflux for 6 hours in nitrogen, cooled, and filtered, giving an intractable solid (49 mg.). After extraction with benzene, the filtrate was acidified. The precipitate (100 mg.) was filtered and crystallised from ethyl methyl ketone in colourless needles, m. p. 219—222° (decomp.) not depressed by mixture with 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid. Ether-extraction of the aqueous acid filtrate and recovery gave a gum with a phenolic smell. Distillation *in vacuo* followed by extraction with boiling light petroleum gave a soluble phenolic fraction which gave a blue colour with Gibbs' reagent.

Attempted oxidation of 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione and 7-chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione with chromic acid failed. Small amounts of unchanged starting materials were the only compounds isolated.

Catalytic Reduction of 7-*Chloro*-4 : 6-*dimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione*.—(*a*) The ketone (322 mg.) in ethanol (30 ml.) was hydrogenated with Raney nickel (*ca.* 1·0 g.) in an atmosphere of hydrogen at room temperature and pressure (absorption: 2 mols. in 20 minutes). The gummy product obtained by removal of the catalyst and solvent was chromatographed in benzene (50 ml.) on alumina (10 × 2·5 cm.) and fractions showing fluorescence were collected. After two small fractions, ether + 3% of methanol (blue fluorescence) removed 7-*chloro*-4′-*hydroxy*-4 : 6-*dimethoxy*-2′-*methylgrisan*-3-*one* (XIII) (150 mg.) which crystallised from benzene–light petroleum in colourless prisms, m. p. 160° (Found: C, 58·8; H, 5·8; Cl, 10·4. $C_{16}H_{19}O_6Cl$ requires C, 58·8; H, 5·9; Cl, 10·9%). The alcohol was saturated to neutral permanganate, did not react with Brady's reagent, and was insoluble in boiling 3N-sodium hydroxide.

(*b*) The ketone (569 mg.) in ethanol containing 1% of chloroform (40 ml.) was reduced in the presence of Raney nickel (*ca.* 1·0 g.) in ethanol (30 ml.) as described above (absorption: 1 mol. in 50 minutes). The crude product, isolated as described in (*a*), contained a proportion of a nickel complex insoluble in benzene, which was decomposed by shaking it with benzene and dilute sulphuric acid. The organic layer, after concentration to 20 ml., was chromatographed on alumina (10 × 2·5 cm.) and the fluorescent bands were eluted with ether. This yielded 7-*chloro*-4 : 6-*dimethoxy*-2′-*methylgrisan*-3 : 4′-*dione* (XIV) (408 mg.) which crystallised from benzene–light petroleum in colourless needles, m. p. 178—179° (Found: C, 59·3; H, 5·1; Cl, 10·7. $C_{16}H_{17}O_6Cl$ requires C, 59·2; H, 5·3; Cl, 10·9%). The ketone gave a precipitate with Brady's reagent on warming and was saturated to neutral permanganate. It was recovered unchanged after 1 hour's heating with 3N-sodium hydroxide. An increase in the concentration of chloroform led to slower reduction and lower yields.

Oxidation of 7-*Chloro*-4′-*hydroxy*-4 : 6-*dimethoxy*-2′-*methylgrisan*-3-*one*.—The alcohol (40 mg.) in acetic acid (1 ml.) was oxidised by dropwise addition of chromic acid (50 mg.) in acetic acid (0·25 ml.) and water (0·1 ml.). The mixture was warmed on the steam-bath between additions of the reagent, and finally, after one hour at room temperature, was diluted with water (10 ml.) and filtered. Crystallisation of the product (18 mg.) from benzene–light petroleum gave 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione, m. p. 176—178° not depressed by mixture with material obtained in the previous experiment.

7-*Chloro*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3-*one* (II).—(i) *Alkaline hydrolysis.* (*a*) No reaction took place in refluxing 25% sodium hydroxide (3 hours).

(*b*) The compound (274 mg.) and 20% aqueous alcoholic potassium hydroxide (40 ml.) were heated together under reflux in nitrogen for 6½ hours. After cooling, the neutral product (188 mg.) was filtered off and the filtrate, after extraction with benzene and ethyl acetate, was acidified with hydrochloric acid. Extraction with benzene and recovery gave an acid (5 mg.), m. p. 205—209° (decomp.), depressed to 191—192° by mixture with 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid [m. p. 210—215° (decomp.)]. The neutral product was chromatographed in benzene (15 ml.) on alumina (15·5 × 2 cm.). On elution with ether–light petroleum (1 : 1) a band of violet fluorescence separated and was collected (eluate I), followed by one of little fluorescence (eluate II). A second violet band was eluted with ether (eluate III). On evaporation the eluates gave (all crystallised from light petroleum): (I) *compound A* (44 mg.), rods and needles, m. p. 165—166° [Found: C, 62·2, 62·5; H, 6·4, 6·5; Cl, 10·7, 8·4; OAlkyl, calc. as OMe, 24·7 $C_{18}H_{23}O_6Cl$ requires C, 62·2; H, 6·3; Cl, 9·7; apparent OMe (2OEt, 1OMe), 25·2%]; (II) *compound B* (20 mg.), cubes, m. p. 172—173° (Found: C, 61·3; H, 6·0; Cl, 10·1. $C_{18}H_{21}O_6Cl$ requires C, 61·3; H, 6·0; Cl, 10·05%); and (III) *compound C* (51 mg.), needles, m. p. 162—163°, $[\alpha]_D^{15}$ +134° (*c.* 0·6 in acetone) [Found: C, 61·3; H, 6·0; Cl, 9·5; OAlkyl calc. as OMe, 24·35. $C_{18}H_{21}O_6Cl$ requires C, 61·3; H, 6·0; Cl, 10·05; apparent OMe (1OEt, 2OMe), 26·1%].

A mixture of compounds B and C melted at 168—172° but the m. p. of compound C could not be raised above 162°. Material of m. p. 172° was obtained from only two of three experiments and it is probable that compounds B and C are isomeric monoethoxy-derivatives. The infra-red spectra of compounds B and C (see Table 1) were indistinguishable and almost identical with the infra-red spectrum of 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one. The spectrum of compound A showed slight differences. The products were stable to alkali, saturated to neutral permanganate and not ketonic to Brady's reagent.

(ii) *Acidic hydrolysis.* (*a*) Hydrolysis with ethanolic N-sulphuric acid gave an intractable gum which was shown to be a mixture by the infra-red spectrum.

(*b*) The compound (500 mg.) was heated under reflux with acetic acid (40 ml.) and water (10 ml.) for 2 hours. Evaporation *in vacuo* gave a solid (334 mg.) which was chromatographed in benzene (20 ml.) on alumina (8 × 1·5 cm.). A blue fluorescent band was eluted with benzene + 1% of methanol and gave on evaporation 7-*chloro*-4 : 6-*dimethoxy*-6′-*methylgrisan*-3 : 2′-*dione*

(XV) (261 mg.) which crystallised from benzene–light petroleum in colourless needles, m. p. 204—205° (Found: C, 59·5; H, 5·2; Cl, 11·1; OMe, 21·1. $C_{16}H_{17}O_6Cl$ requires C, 59·2; H, 5·3; Cl, 10·9; 2OMe, 19·1%). The compound was saturated to neutral permanganate and insoluble in cold sodium hydroxide. It dissolved on warming (see below). It was identical (mixed m. p. and infra-red spectrum) with the ketone $C_{16}H_{17}O_6Cl$ (XVIII) recorded in Part I.

(iii) *Oxidation.* (*a*) The compound was not attacked by alkaline hydrogen peroxide at room temperature or at 100°.

(*b*) A warm solution of the compound (500 mg.) in acetic acid (9 ml.) was treated in portions with chromic oxide (1·5 g.) in acetic acid (9 ml.) and water (4 ml.) (spontaneous refluxing). When addition was complete the solution was heated under reflux for 5 minutes, cooled, diluted with water (20 ml.), and extracted with benzene. The extract was washed with sodium carbonate solution and evaporated, giving a gum which was washed with a little ether, thus yielding a solid (52 mg.). The solid was chromatographed in benzene (3 ml.) on alumina (10 × 1·0 cm.). A narrow band with violet fluorescence was eluted with ether and discarded. Further elution with ether + 1% of methanol eluted first a faint dark violet fluorescing band, giving on evaporation *7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione* (XII) (30 mg.) and then a band of blue fluorescence which on evaporation gave griseofulvin (9 mg.), identified by mixed m. p. and infra-red spectrum.

The dione (XII) crystallised from ethanol in colourless needles. The purest specimens obtained by this method melted at 273° (decomp.) although material of higher m. p. was obtained by a different method (see below) [Found: C, 59·7; H, 4·8; Cl, 10·6; OMe, 16·0%; *M* (micro-Rast), 328. $C_{16}H_{15}O_6Cl$ requires C, 59·5; H, 4·7; Cl, 11·0; 2OMe, 19·2%; *M*, 322·5). The dione did not react with Brady's reagent and was unsaturated to neutral permanganate. It was insoluble in cold 3N-sodium hydroxide but decomposed on warming therein.

7-Chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione was also obtained by acid hydrolysis of 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgrisan-3 : 2′-dione (see below) and as a minor product from the reduction of 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione (Part V). The m. p.s of mixtures were not depressed and the infra-red spectra were identical. They were also identical with a specimen obtained by reduction of griseofulvin with aluminium *iso*propoxide (see below).

Alkaline Hydrolysis of 7-Chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′-dione.—The ketone (240 mg.) was refluxed with N-sodium hydroxide (20 ml.) in nitrogen for 2 hours. After cooling, undissolved material (16 mg.) was rejected, and the filtrate was acidified with concentrated hydrochloric acid. After storage of the solution in the refrigerator, the sticky solid was filtered off, washed with water, and dissolved in benzene. Recovery gave *7-chloro-4*(or 6)-*hydroxy-6*(*or* 4)-*methoxycoumaran-3-one-2-5′-hexanoic acid* (XVI) as a colourless solid (184 mg.) which after repeated crystallisation from ethyl methyl ketone–light petroleum had m. p. 177—179° [Found: C, 54·3, 55·1; H, 5·2, 5·5; Cl, 11·0; OMe, 12·2%; equiv. (potentiometric titration), 150. $C_{15}H_{17}O_6Cl$ requires C, 54·8; H, 5·2; Cl, 10·8; 1OMe, 9·4%; equiv. (dibasic acid), 164]. The acid was soluble in aqueous sodium hydrogen carbonate, and gave a weak brown colour with ferric chloride, intensified by addition of water. It gave a positive Millon's but negative Gibbs' reaction, did not couple with diazotised amines, and was slowly attacked by neutral permanganate. It did not react with Brady's reagent.

7-Chloro-4 : 6 : 4′-trimethoxy-6′-methylgrisan-3 : 2′-dione (VIII).—(a) The ketone was insoluble in cold 3N-sodium hydroxide but partly dissolved when heated, giving a yellow solution.

(b) *Acid hydrolysis.* The ketone (60 mg.), ethanol (12 ml.), and 2N-sulphuric acid (15 ml.) were heated under reflux for 6 hours. The solid [18 mg.; m. p. *ca.* 240° (decomp.)], obtained by concentration *in vacuo* and filtration, was further purified by passage of a solution in benzene through a short column of alumina, elution being completed with ether + 1% of methanol. Crystallisation of the recovered material from ethanol gave 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione as colourless needles, m. p. 275—277° (decomp.). The identity with material obtained by oxidation of 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one was confirmed by mixed m. p. and the infra-red spectrum.

7-Chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one (VII).—This was insoluble in boiling 3N-sodium hydroxide.

Reduction of 7-Chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione.—(*a*) In the presence of Raney nickel in ethanol, hydrogen (3 mols.) was absorbed during 10 minutes at room temperature and pressure, but the product could not be purified.

(*b*) A solution of the ketone (45 mg.) in ethanol (40 ml.) containing chloroform (1%) was shaken with hydrogen in the presence of Raney nickel (*ca.* 1·0 g.) in ethanol (40 ml.) at room

temperature and pressure. Hydrogen (1·5 mols.) was absorbed in 5 minutes. At this stage, rapid gas evolution began and the reaction was stopped. After filtration and recovery, the crude product which was only partly soluble in benzene, was shaken with benzene and dilute sulphuric acid. The solid (12 mg.) obtained from the benzene layer by evaporation and trituration of the resultant gum with ether crystallised from ethyl acetate in colourless prisms, m. p. 200—201°, identical (mixed m. p. and infra-red spectrum) with 7-chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′-dione.

Hydrogenation of 7-*Chloro*-4 : 6-*dimethoxy*-2′-*methylgrisan*-3 : 4′ : 6′-*trione in the Presence of Palladium Black* [Dr. J. MacMillan].—The trione (1·0 g.) in acetic acid (50 ml.) was hydrogenated in presence of palladium black at room temperature and pressure (1·5 mols. absorbed in 2¼ hours). After filtration and recovery the residual colourless gum, on trituration with light petroleum, gave a gum which could not be crystallised or purified by chromatography. It was neutral, ketonic, and unsaturated to potassium permanganate. The crude product (200 mg.) was dehydrated by heating it under reflux for 2 minutes with concentrated hydrochloric acid (0·2 ml.) and acetic acid (2·0 ml.). Subsequent dilution with water gave a solid which, crystallised from dilute ethanol, had m. p., alone or mixed with 7-chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione, 178° (Found : C, 59·55; H, 5·0. Calc. for $C_{16}H_{15}O_5Cl$: C, 59·5; H, 4·7%). The dinitrophenylhydrazone crystallised from nitrobenzene–methanol in orange needles, m. p. and mixed m. p. with 7-chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione dinitrophenylhydrazone, 283—284° (decomp.) (Found : C, 53·0; H, 3·9; N, 11·5. Calc. for $C_{22}H_{19}O_8N_4Cl$: C, 52·9; H, 3·8; N, 11·1%).

Reduction of Griseofulvin with Aluminium iso*Propoxide* [Dr. M. A. T. Rogers].—Griseofulvin (0·5 g.) was reduced with *iso*propyl alcohol (50 ml.; dried by distillation from aluminium *iso*propoxide) and aluminium *iso*propoxide (1·0 g.). After 6 hours the solvent was removed, the residue was stirred with 2N-hydrochloric acid, and the residual solid was washed and dried (0·4 g.; m. p. 216—240°). Crystallisation from ethanol gave colourless needles, m. p. 275° (slow decomp.), and from toluene–light petroleum long flattened needles, $[\alpha]_D^{21}$ +281° (*ca.* 0·98 in chloroform), identical (mixed m. p. and infra-red spectrum) with 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione prepared by other methods. These results were not always reproducible and sometimes griseofulvin was recovered unchanged.

The author thanks Mr. J. F. Grove and Dr. L. A. Duncanson for the determination of the infra-red spectra and Dr. A. F. Wells, Imperial Chemical Industries Limited, Dyestuffs Division, for the *X*-ray powder comparison of specimens of 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid.

Imperial Chemical Industries Limited, Butterwick Research Laboratories,
The Frythe, Welwyn, Herts. [*Received, February 22nd,* 1952.]

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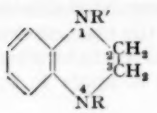
765. *The Chemotherapy of Filariasis. Part I. Monoacyl Derivatives of* 1 : 2 : 3 : 4-*Tetrahydroquinoxaline.*

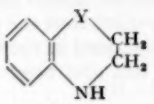
By J. S. Morley.

Contrary to previous statements, monoacyl derivatives of tetrahydroquinoxaline may readily be obtained by direct reaction between the base and an acylating agent. At relatively high pH's the yields of monoacyl derivatives (from equimolecular proportions of reactants) exceed 70%. Below pH 5, the yield drops rapidly and disubstitution predominates; this corresponds with a marked increase in ionisation of the base which has been used to interpret the effect. Methylation of the monoacyl derivatives gave the 1-acyl-4-methyl derivatives which were also prepared by acylation of tetrahydro-1-methylquinoxaline.

Apart from the antimonial drugs, the most promising chemicals for treatment of filarial infections have been (*a*) certain derivatives of piperazine (Stewart, Turner, Denton, Kushner, Brancone, McEwen, Hewitt, and Subbarow, *J. Org. Chem.*, 1948, **13**, 134, 144) and (*b*) cyanine dyes and compounds of cyanine-like structure (Welch, Peters, Bueding, Valk, and Higashi, *Science*, 1947, **105**, 486). Of these, the piperazines, especially "Hetrazan" (1-diethylcarbamyl-4-methylpiperazine), have been by far the more useful in the treatment of human cases (for a comparative review of the merits of available canine and human filari-

cides see Otto and Maren, *Amer. J. Hyg.*, 1950, **51**, 385). A series of investigations is therefore planned, designed to throw light on certain features of the piperazine molecule that may be essential for biological activity. Initially, it seemed desirable to evaluate the effect of unsaturation in the piperazine ring on biological activity; the present paper describes the preparation of a tetrahydroquinoxaline analogue (I; R = Me, R′ = CO_2Et) of the active 1-carbethoxy-4-methylpiperazine, where single unsaturation has been introduced at the expense of an additional ring, and of various other monoacyl derivatives of tetrahydroquinoxaline and its *N*-methyl derivative. It is a pleasure to acknowledge the helpful advice and encouragement given by Dr. F. Hawking and Miss W. A. F. Weber of the National Institute for Medical Research, who have kindly undertaken the biological work. The latter will be published later.


(I)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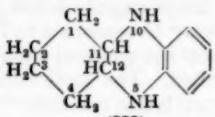
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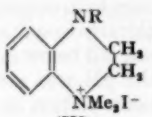
(IV)

The preparation of the requisite monoacyltetrahydroquinoxalines (I; R = H, R′ = Acyl) was of interest in that reaction between the base and various acylating agents has been stated to give solely disubstituted products. Thus Meisenheimer and Wieger (*J. pr. Chem.*, 1921, **102**, 49) obtained only diacetyl- and dibenzoyl-tetrahydroquinoxaline. Cavagnol and Wiselogle (*J. Amer. Chem. Soc.*, 1947, **79**, 795) were unable to isolate any of the monosubstituted product on use of acetic anhydride, acetyl chloride, keten, acetamide, or benzoyl chloride under varied conditions; the method of Moore, Boyle, and Thorn (*J.*, 1929, 39) for monocarbethoxylation of piperazines and ethylenediamines at controlled pH led, similarly, only to dicarbethoxytetrahydroquinoxaline and starting material. These results seemed anomalous in the light of experience with piperazine (Moore, Boyle, and Thorn, *loc. cit.*; Baltzly, Buck, Lorz, and Schön, *J. Amer. Chem. Soc.*, 1944, **66**, 263; Brancone *et al.*, *loc. cit.*) on one hand, and dihydrophenazine (following paper) on the other, since in both these cases monosubstitution had been observed under suitable conditions. We therefore reinvestigated the reactions involving tetrahydroquinoxaline, using equimolecular proportions of the base and acylating agent. In all cases, an appreciable amount of monosubstitution was found to take place, a ready separation of the mono- and disubstituted products and unchanged base being possible because of their marked differences in basicity. Acetic anhydride in acetic acid gave 1-acetyl- (I; R = H, R′ = Ac) (47% based on tetrahydroquinoxaline) and 1 : 4-diacetyl-tetrahydroquinoxaline (I; R = R′ = Ac) (15%) and unchanged base (28%); chloroformic ester in ethanol gave 1-carbethoxy- (20%) and 1 : 4-dicarbethoxy-tetrahydroquinoxaline (21·5%) and unchanged base (45%); and benzoyl chloride in aqueous acetone gave 1-benzoyl- (20%) and 1 : 4-dibenzoyl-tetrahydroquinoxaline (39%) and unchanged base (34%).

The effect of solvent was next studied, in the carbethoxylation and acetylation reactions (see Table I). In the reaction with chloroformic ester, the proportion of mono- to dicarbethoxytetrahydroquinoxaline remains fairly constant but undergoes a slight, yet significant, decrease in passing towards a more acidic solvent. The same decrease is evident on comparing the reaction with acetic anhydride in ethanol with that in acetic acid.

At first sight, these results appeared surprising since the suggestion that a lower pH

TABLE I. *Carbethoxylation and acetylation of tetrahydroquinoxaline.*

Carbethoxylation			Acetylation			Carbethoxylation		
	Substitution (%) *		Reagent	Substitution (%) *			Substitution (%) †	
Solvent	Mono	Di	and solvent	Mono	Di	pH	Mono	Di
C_5H_5N	54	46	Ac_2O–EtOH	100	0	7	75	0
$COMe_2$	50	50	Ac_2O–AcOH	72	28	6	75	0
EtOH	50	50	AcCl–EtOH	38	62	5	75	Trace
AcOH	33	67	AcCl–AcOH	32	68	4	30	51
						3	25	58

* As % (wt.) of total acylated product isolated. † Yields, based on tetrahydroquinoxaline.

favours disubstitution is the reverse of what is generally believed to hold in the piperazine series (cf., *e.g.*, Moore, Boyle, and Thorn, *loc. cit.*), the explanation there advanced being that a decrease in pH increases the ionisation of the monosubstituted piperazine, yielding a cation which is resistant to further substitution. Nevertheless, our results were supported by the fact that the yields of monosubstituted tetrahydroquinoxaline in those acylations involving the elimination of halogen acid (carbethoxylation and benzoylation) were much lower than in those involving acetic anhydride. The latter point was strikingly illustrated by substituting acetyl chloride for acetic anhydride in the acetylation reaction under otherwise identical conditions (see Table I). Final test, by conducting the carbethoxylation at various controlled pH's (Table I) proved conclusively that monosubstitution is at its maximum at relatively high pH's. Not only does the proportion of mono- to di-carbethoxytetrahydroquinoxaline fall off rapidly below pH 5, but the actual yield of monocarbethoxytetrahydroquinoxaline may be increased to 75% provided that the pH of the reaction does not fall below 5, as against the yields of about 25% obtained in the original reactions where the pH was not controlled. The same conclusion has also been shown to apply to the benzoylation and the acetylation reaction.

Now, it had been surmised qualitatively that there was a marked drop in basicity of tetrahydroquinoxaline on monoacylation and potentiometric determination of pK_a values in 50% ethanol (Table 2) confirmed this quantitatively. From the results, the degree of ionisation of the various compounds concerned was calculated for different pH values. Between pH 3 and 5 there is a marked change in ionisation of tetrahydroquinoxaline itself, but the ionisation of its monacyl derivatives is virtually unaffected (almost complete non-ionisation); for the latter the change occurs between pH 1 and 3. Of the species involved in the acylation reactions, those predominant are B (un-ionised tetrahydroquinoxaline) and BX (un-ionised monoacyltetrahydroquinoxaline) above pH 4·5, and BX and BH^+ (the tetrahydroquinoxalinium ion) between pH 2 and 4·5. Now, it seems reasonable to assume that the reactivity (towards acylating agents) of the species will fall off in the order: $B > BX > BH^+$. In conformity, the drain of electrons from the potentially reacting NH group (see II) would, at any rate, be expected to be greatest in BH^+ (II; Y = $>NH_2^+$) less in BX (II; Y = >N·Acyl), and smallest in B (II; Y = >NH). This being so, reaction above pH 4·5 will involve, primarily, the species B (leading to monosubstitution), whilst below pH 4·5 reaction with species BX (leading to disubstitution) will be more favoured.

TABLE 2. *Determination of basic strength.*

Compound	Derivative	Concn. (mole./l.) × 10^3	Solvent	Temp.	pK_a
Tetrahydroquinoxaline	—	?	H_2O (?)	?	4·84 [a]
,, ...	—	9·02	50% aq. EtOH	24—25°	4·60
,, ...	Monocation	?	H_2O (?)	?	(1·17) [a]
,, ...	1-CO_2Et	6·56	50% aq. EtOH	24—25	2·21 [b]
,, ...	1-SO_2Ph	4·72	,,	,,	1·92
,, ...	1-Ac	8·10	,,	,,	1·84
trans-Octahydrophenazine ...	— *	4·96	50% aq. EtOH	24—25	4·62
,, ...	—	6·22	,,	,,	4·62 [b]
,, ...	5-SO_2Ph *	3·92	,,	,,	2·04
o-Phenylenediamine	—	1·28—10·3	H_2O	20	4·47 [c]
,, ...	—	1·28—5·15	50% aq. MeOH	,,	4·42 [c]
,, ...	Monocation	10·5	H_2O	,,	(0·02) [c]
,, ...	,,	2·63—5·25	50% aq. MeOH	,,	(0·67) [c]

[a] Cavagnol and Wiselogle, *loc. cit.* [b] By titration of the hydrochloride with sodium hydroxide. [c] Kuhn and Zumstein, *Ber.*, 1926, **59**, 488; Kuhn and Wasserman, *Helv. Chim. Acta*, 1928, **11**, 20. * Part II, following paper.

A fairly satisfactory qualitative interpretation of the course of the reactions is thus arrived at (discussion of the rather complicated kinetics does not appear justified in view of the limited experimental data). It may be noted it should apply equally to acylation reactions of other diacidic bases whose pK_a values (of the base and of its acyl derivatives) correspond, approximately, to those of tetrahydroquinoxaline (see Table 2). Preliminary results indicate that this is in fact so in the cases of *trans*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydrophenazine (III) and *o*-phenylenediamine.

Methylation of the monoacyl derivatives of tetrahydroquinoxaline gave the compounds (I; R = Me, R′ = Ac, Bz, CO_2Et), identical with specimens prepared by direct acylation of 1-methyltetrahydroquinoxaline. These reacted slowly in ethanol with excess of methyl iodide, giving the quaternary salts (IV; R = Ac or CO_2Et); for biological comparison, the methiodide of "Hetrazan" was prepared.

In contrast with the ready reaction of (I; R = R′ = H or Me) with acetyl chloride, benzoyl chloride, and chloroformic ester, neither compound reacted with diethylcarbamyl chloride under a variety of conditions. This acid chloride reacts smoothly with a variety of piperazines (Brancone *et al.*, *loc. cit.*) and with piperidine (unpublished work), though Hurd and Spence (*J. Amer. Chem. Soc.*, 1927, **49**, 266) report that it does not react with sodium azide in benzene and that only diethylamine hydrochloride is obtained by reaction with hydrazine in methanol. Other routes to (I; R = Me, R′ = $CO{\cdot}NEt_2$) are being investigated.

Experimental

M.p.s are uncorrected.

1 : 2 : 3 : 4-*Tetrahydroquinoxaline*.—This base was prepared in excellent yield by hydrogenation of quinoxaline (Cavagnol and Wiselogle, *loc. cit.*) and also by the one-stage synthesis from catechol and ethylenediamine (Merz and von Ris, *Ber.*, 1887, **20**, 1191; cf. Almond and Mann, *J.*, 1951, 1906). The difficulties experienced by Cavagnol and Wiselogle (*loc. cit.*) in the latter reaction were not encountered; the following procedure gave the stated yield of pure product consistently, and was preferred as a rapid and convenient route to moderate quantities of the base: Commercial catechol (24 g.) and ethylenediamine hydrate (20 ml.) were heated in a sealed tube at 200—210° for 15 hours, and the product was melted into water (250 ml.) with mechanical stirring. The resulting suspension was then extracted thrice with benzene, and the combined extracts were washed with N-sodium hydroxide, then with water, dried (K_2CO_3), and concentrated; addition of light petroleum (b. p. 60—80°) gave pale yellow crystals of almost pure tetrahydroquinoxaline (average yield 47% based on catechol), m. p. 97—98°. A further crop (5%) was obtained by concentration of the mother-liquors. The hydrochloride, prepared by passing dry hydrogen chloride into a solution of the base in dry acetone, separated from ethanol–ether under nitrogen in colourless needles, m. p. 167—169°, slowly becoming pink in air.

Acetylation with Acetic Anhydride.—(*a*) To a solution of tetrahydroquinoxaline (5 g.) in glacial acetic acid (25 ml.) at 27—30° acetic anhydride (3·53 ml.) was aed droddpwise during 5 minutes with mechanical stirring and cooling as necessary. After ½ hour's stirring at room temperature, the solution was diluted with water (100 ml.) and made alkaline (litmus) with concentrated aqueous ammonia, the pH brought to 4—5 by dropwise addition of concentrated hydrochloric acid, and the resulting suspension extracted with ether (3 × 85 ml.). The ethereal extracts were washed with 20% aqueous acetic acid (4 × 25 ml.) and once with water (25 ml.) (combined washings A), dried, and neutralised (K_2CO_3), then evaporated to 10 ml., giving **1-*acetyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*** (3·10 g.), m. p. 108—109°, which formed brittle, pale ginger-coloured prisms, m. p. 109—110°, from dry benzene–light petroleum (b. p. 60—80°); the mixed m. p. with tetrahydroquinoxaline was 72—74° (Found: C, 67·95; H, 6·7; N, 16·1. $C_{10}H_{12}ON_2$ requires C, 68·2; H, 6·9; N, 15·9%). This monoacetyl derivative was moderately soluble in hot water and gave colourless prisms on cooling; it was more soluble in cold dilute hydrochloric acid than in water.

The original aqueous phase from the ether-extraction was made acid to Congo-red with concentrated hydrochloric acid and extracted with benzene (extracts B), then basified with sodium hydroxide, and re-extracted with benzene (extracts C). Extracts B, after drying (K_2CO_3) and evaporation, gave a colourless residue of 1 : 4-diacetyltetrahydroquinoxaline (0·58 g., 7·15%), m. p. and mixed m. p. 143—144°. Extracts C contained only a little oil (0·3 g.) which was mostly tetrahydroquinoxaline. The bulk of the unchanged tetrahydroquinoxaline was present in the washings A, and was isolated by basification and extraction with benzene; the residual oil (2·4 g.) from the evaporated extracts gave tetrahydroquinoxaline hydrochloride (1·8 g., 28·4%) by treatment with dry hydrogen chloride in ethanol.

By bringing the basified reaction mixture directly to pH 3 with concentrated hydrochloric acid and extraction with benzene, the yield of diacetyltetrahydroquinoxaline in this reaction was ascertained as 15·4%.

(*b*) In ethanol (50 ml.), under conditions otherwise identical with those described in (*a*),

the sole product was the monoacetyltetrahydroquinoxaline (6·3 g., 96%), m. p. and mixed m. p. 107—109°, isolated by dilution with water (150 ml.), basification (sodium hydroxide), and extraction with benzene.

(*c*) When tetrahydroquinoxaline (1 g.) was added in portions to acetic anhydride (1·50 ml., equiv. to 2 moles per mole of base) at 35—40°, and left for 2 hours at room temperature, the product, isolated by basification and extraction with benzene, was wholly 1 : 4-diacetyl-1 : 2 : 3 : 4-tetrahydroquinoxaline (1·05 g.), which formed small colourless warts (from ethyl acetate), m. p. 143—144° (Ris, *Ber.*, 1888, **21**, 378, gives m. p. 144°; Cavagnol and Wiselogle, *loc. cit.*, give m. p. 147—147·5°) [Found: C, 66·05; H, 6·45; N, 12·7%; *M* (ebullioscopic), 209. Calc. for $C_{12}H_{14}O_2N_2$: C, 66·0; H, 6·5; N, 12·8%; *M*, 218). This compound was easily soluble in hot water and in organic solvents other than ether and light petroleum; it was, curiously, appreciably more soluble in dilute acids than in water.

(*d*) The diacetyl compound (1·08 g.), m. p. 143—144°, and a further crop (0·18 g.) separating gradually from the mother-liquors, were likewise obtained by refluxing of tetrahydroquinoxaline (1 g.) and acetic anhydride (1·5 ml.) for 5 minutes, and followed by addition to aqueous ammonia.

Carbethoxylation.—Ethyl chloroformate (4·76 ml., 0·05 mol.) was added dropwise during ¼ hour with mechanical stirring to a suspension of tetrahydroquinoxaline (6·7 g., 0·05 mol.) in ethanol (50 ml.); the temperature, originally 15°, was allowed to rise to 20—22°, and kept within these limits by occasional cooling. The solution was then stirred for 1 hour at room temperature (during which the temperature dropped to 15°), water (5 ml.) was added, and the stirring continued for ½ hour at 30°. Dilution with water (100 ml.) and extraction with ether (3 × 125 ml.) left an aqueous phase which, after basification with sodium hydroxide, gave unchanged tetrahydroquinoxaline (3·02 g., 45%), m. p. 90—92°, isolated by exhaustive extraction with benzene. The combined ethereal extracts were washed with water (2 × 25 ml.; these washings were combined with the aqueous phase above), dried ($MgSO_4$), and evaporated, giving an oil, which was dissolved in benzene (50 ml.) and treated with an excess of hydrogen chloride in dry ether. 1-*Carbethoxy*-1 : 2 : 3 : 4-*tetrahydroquinoxaline hydrochloride* (2·5 g., 20·6%), m. p. 149—150°, was thereby precipitated as an oil which rapidly crystallised when scratched; the pure compound formed clusters of soft colourless needles, m. p. 151—152°, from ethanol–ether (Found: C, 54·4; H, 6·0; N, 11·6. $C_{11}H_{14}O_2N_2$,HCl requires C, 54·45; H, 6·2; N, 11·55%); this dissociated into the base (an oil) when suspended in water. The benzene–ether mother-liquors from this hydrochloride were then shaken with 2N-aqueous ammonia, and the organic layer was combined with two extracts of the aqueous layer with ether; after being washed with water and dried (K_2CO_3), the extracts were evaporated, yielding an oil, which distilled almost completely at 176°/0·3 mm. The distillate (3·0 g., 21·5%) crystallised after being scratched under light petroleum (b. p. 40—60°), giving 1 : 4-dicarbethoxy-1 : 2 : 3 : 4-tetrahydroquinoxaline (2·8 g.) m. p. 40—41°, which formed large, colourless prisms [from light petroleum (b. p. 40—60°)], m. p. 40·5—42°, unchanged after recrystallisation from water (in which the compound was only sparingly soluble) [Cavagnol and Wiselogle, *loc. cit.*, give m. p. 42—44° (anhyd.), and describe a trihydrate as an oil] (Found: C, 60·6; H, 6·4; N, 10·0. Calc. for $C_{14}H_{18}O_4N_2$: C, 60·4; H, 6·5; N, 10·05%).

In other experiments when the chloroformic ester was added at 18—30°, the solution stirred for ½ hour at 20—30°, then for 10 minutes at 35—40°, and a further ¼ hour with water (5 ml.) at 35—40°, the yield of monocarbethoxy-derivative was 24%.

The reactions in solvents other than ethanol were carried out similarly, and the products were separated by application of the same principles.

Carbethoxylation at Controlled pH.—The reaction vessel consisted of a 400-ml. beaker, fitted with mechanical stirring and a thermometer, into which projected sealed glass and dip-type calomel electrodes working in conjunction with a Cambridge Instrument Company pH meter (bench type). After standardisation, tetrahydroquinoxaline (1 g.), dissolved in ethanol (100 ml.) and B.D.H. Universal Buffer Solution (100 ml.), was added, and the pH of the solution brought to the desired value by addition of concentrated alkali or acid. An equimolar proportion of chloroformic ester (0·71 ml.) was then added, dropwise, with stirring, through a microburette (time of addition *ca.* ½ hour; temp. 25°); reaction was rapid but the desired pH was easily maintained within ±0·02 unit, by cautious addition of 2N-sodium hydroxide while each drop of acid chloride was reacting. The solution was finally stirred for a further ¼ hour, whereafter the pH was brought to 2—3 by addition of concentrated hydrochloric acid and the products were isolated as described in the previous experiment.

Benzoylation.—A solution of tetrahydroquinoxaline (5·0 g.) in acetone (50 ml.) and water (10 ml.) was stirred and treated dropwise during ¼ hour at 25—30° with freshly distilled benzoyl

chloride (4·30 ml.). Water (10 ml.) was added, the suspension stirred for a further ½ hour at room temperature and then filtered, giving pure 1 : 4-dibenzoyl-1 : 2 : 3 : 4-tetrahydroquinoxaline (5·0 g., 39%), which formed colourless cubes, m. p. 204—205°, from acetone [Meisenheimer and Wieger (*loc. cit.*) give m. p. 201—202°; Cavagnol and Wiselogle (*loc. cit.*) give m. p. 206—207°] (Found: N, 8·3. Calc. for $C_{22}H_{18}O_2N_2$: N, 8·2%).

The filtrate was evaporated under reduced pressure on the steam-bath until a turbidity set in, water added to bring the volume to 120 ml., and the suspension extracted with benzene. The combined extracts were washed with water (washings A), followed by N-sodium hydroxide, and finally water, dried (K_2CO_3), and evaporated to 20 ml. under reduced pressure; 1-*benzoyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* (1·1 g.), m. p. 147—148°, separated on cooling, and a further crop (0·7 g.; total yield of crude product, 20%) after addition of light petroleum (b. p. 40—60°) to the mother-liquors. The pure compound formed colourless prisms, m. p. 152—153°, from benzene, which were very much more soluble in acetone than the dibenzoyl derivative (Found: N, 12·1. $C_{15}H_{14}ON_2$ requires N, 11·75%).

Unchanged tetrahydroquinoxaline (1·7 g., 34%) was recovered from the acid aqueous phase from the above extraction and from washings A, by basification with sodium hydroxide and extraction with benzene.

1 : 2 : 3 : 4-*Tetrahydro*-1-*methylquinoxaline*.—Finely-powdered tetrahydro-1-methyl-4-phenylsulphonylquinoxaline (15 g.) [Cavagnol and Wiselogle (*loc. cit.*)] was added portionwise to concentrated sulphuric acid (15 ml.) with stirring at 45—50°, and the stirring continued at room temperature until all the solid had dissolved. The blue-green solution was then warmed on the steam-bath for 10 minutes and basified in the cold with ice and 40% sodium hydroxide solution, enough water was added to redissolve precipitated inorganic salts, and the mixture extracted with benzene. Distillation of the residue from the dried (K_2CO_3), evaporated extracts gave tetrahydro-1-methylquinoxaline (6·4 g., 83%), b. p. 108°/2 mm., which slowly darkened in air. When a solution in acetone (150 ml.) was saturated with dry hydrogen chloride, the *monohydrochloride* (8·0 g.) was precipitated as a colourless solid, which formed large, prismatic needles, m. p. 173—174°, when recrystallised from ethanol–ether under nitrogen (Found: C, 58·6; H, 6·9. $C_9H_{12}N_2$,HCl requires C, 58·55; H, 7·1%); in air, the solution suddenly became red during the recrystallisation, and the crystals were tinged red.

1-*Acetyl*-1 : 2 : 3 : 4-*tetrahydro*-4-*methylquinoxaline*.—(*a*) Tetrahydro-1-methylquinoxaline (0·8 g.) and acetic anhydride (3 ml.) were gently refluxed for ½ hour, the excess of anhydride was decomposed with water, and the solution basified with aqueous ammonia; the acetyl compound, isolated by ether-extraction, was a colourless oil which, when dissolved in dry benzene (20 ml.) and treated with dry hydrogen chloride, gave a *monohydrochloride* (0·7 g.), which crystallised from ethanol–ether in colourless prisms, m. p. 154—155° (Found: C, 57·95; H, 6·5; N, 12·1. $C_{11}H_{14}ON_2$,HCl requires, C, 58·25; H, 6·7; N, 12·35%).

(*b*) 1-Acetyltetrahydroquinoxaline (1 g.), anhydrous sodium carbonate (1·2 g.), and methyl iodide (0·71 ml.) were gently refluxed in ethanol (10 ml.) for 5 hours under nitrogen at a slight positive pressure (5 cm. mercury). The ethanol was then removed and the residue digested with dry benzene (4 × 10 ml.); 1 acetyltetrahydro-4-methylquinoxaline (0·91 g.) was obtained as an oil from the filtered and evaporated digests, and gave a hydrochloride identical with that prepared by method (*a*).

1-*Acetyl*-1 : 2 : 3 : 4-*tetrahydro*-4 : 4-*dimethylquinoxalinium Iodide*.—(*a*) When the above acetyl derivative (0·8 g.) was heated under gentle reflux with methyl iodide (3 ml.) in ethanol (5 ml.) for 7 hours, the pure *methiodide* (0·32 g.) separated in the hot, forming soft, colourless, prismatic needles, m. p. 184—185° (decomp.), from ethanol (Found: C, 43·05; H, 5·1. $C_{12}H_{17}ON_2I$ requires C, 43·4; H, 5·2%).

(*b*) The crude methiodide (0·18 g.) separated slowly after 1-acetyltetrahydroquinoxaline (0·75 g.) had been heated with methyl iodide (3 ml.) in methanol (10 ml.) under reflux for 13 hours; recrystallisation from ethanol (20 ml.) (charcoal) gave the pure compounds (0·11 g.), identical in m. p. and mixed m. p. with the above specimen.

1-*Carbethoxy*-1 : 2 : 3 : 4-*tetrahydro*-4-*methylquinoxaline*.—(*a*) Tetrahydro-1-methylquinoxaline hydrochloride (1 g.), ethyl chloroformate (0·60 ml., rather more than one mol.), and sodium hydrogen carbonate (1·4 g., 3 mols.) in ethanol (10 ml.) were gently refluxed for 4 hours under nitrogen at a slight positive pressure (5 cm. mercury). The ethanol was then evaporated off, the residue extracted with benzene (5 × 10 ml.), and the combined, filtered extracts were evaporated, yielding an oil, which was dissolved in acetone (5 ml.) and saturated with dry hydrogen chloride at 0°; addition of dry ether (5 ml.) gave colourless needles (0·94 g., after ether-washing) of 1-*carbethoxy*-1 ? 2 : 3 : 4-*tetrahydro*-4-*methylquinoxaline hydrochloride*, m. p.

133—134°, not raised after further recrystallisations from ethanol–ether or acetone–ether under nitrogen (Found: C, 55·9; H, 6·9; N, 10·6. $C_{12}H_{16}O_2N_2$,HCl requires C, 56·4; H, 6·7; N, 10·9%). The hydrochloride dissociated in distilled water, yielding the oily base.

(*b*) 1-Carbethoxytetrahydroquinoxaline hydrochloride (0·9 g., rather less than 0·004 mol.), anhydrous sodium carbonate (1·24 g., 0·012 mol.), and methyl iodide (0·5 ml., 0·008 mol.), in ethanol (10 ml.) were gently refluxed for 5 hours under nitrogen. The product, obtained by the procedure described in (*a*), was an oil (0·65 g.), which gave a hydrochloride (0·45 g.), identical in m. p. and mixed m. p. with that described in (*a*). Digestion of the benzene-insoluble fraction with hot ethanol gave the methiodide (0·3 g.) described below.

1-*Carbethoxy*-1 : 2 : 3 : 4-*tetrahydro*-4 : 4-*dimethylquinoxalinium Iodide*.—The crude mixture of mono- and di-carbethoxytetrahydroquinoxaline from the reaction of ethyl chloroformate (2·38 ml.) with tetrahydroquinoxaline (3·35 g.), was heated under reflux with methyl iodide (5 ml.) in ethanol (50 ml.) for 10 hours. After evaporation of the excess of methyl iodide, the crude *iodide* (1·07 g.), m. p. 166—167°, separated slowly, yielding colourless prismatic needles, m. p. 172—173° (decomp.), from ethanol (Found: C, 43·5; H, 5·5; N, 7·3. $C_{13}H_{19}O_2N_2I$ requires C, 43·1; H, 5·3; N, 7·7%).

"*Hetrazan*" *Methiodide*.—"Hetrazan" (1-diethylcarbamyl-4-methylpiperazine) (1 g.), ethanol (5 ml.), and methyl iodide (2 ml.) were gently refluxed for 4 hours. The crude *iodide*, precipitated by the addition of dry ether, formed colourless, brittle, needles, m. p. 159—160° (decomp.), from ethanol–ether, which were easily soluble in cold water (Found: C, 39·0; H, 7·2; N, 12·2. $C_{11}H_{24}ON_2I$ requires C, 38·7; H, 7·1; N, 12·3%).

Determination of pK_a *Values*.—The values given in Table 2 were obtained by the potentiometric method, under the conditions described by Morley and Simpson (*J.*, 1949, 1014), save that ionic strength corrections were applied in each case. At the concentrations employed these are small (0·01—0·04 unit) and were calculated from the approximate formulæ pK_a (corrected) = pK_a (observed) − 0·5 $\sqrt{\mu}$ where μ = the ionic strength of the solution.

The author is greatly indebted to Dr. F. G. Mann and Sir Charles Harington for arranging facilities for commencing this work at Cambridge, and to Dr. F. G. Mann, (the late) Dr. J. C. E. Simpson, and Dr. J. Walker for advice and encouragement.

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766. *The Chemotherapy of Filariasis. Part II.* Monoacyl Derivatives of* 5 : 10-*Dihydro- and* trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*Octahydrophenazine.*

By J. S. Morley.

At room temperature and with excess of acylating agent, 9 : 10-dihydrophenazine gives solely monoacyl derivatives. In contrast, the degree of acylation of *trans*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydrophenazine, like that of tetrahydroquinoxaline, depends upon pH, monoacyl derivatives arising at pH 7 but only diacyl derivatives at pH 3. Details are given of the preparation of phenazine by Ris's method (*Ber.*, 1886, **19**, 2206).

In view of the initial object of these researches, outlined in Part I,* various monoacyl derivatives of di- and *as*-octa-hydrophenazines were of interest. The former may be regarded as doubly, and the latter as singly, unsaturated piperazines (*i.e.*, di- and tetrahydropyrazines), where unsaturation has been introduced at the expense of two additional rings.

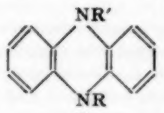
5 : 10-Dihydrophenazine (I; R = R′ = H) is prepared in excellent yield by reduction of phenazine (Claus, *Ber.*, 1875, **8**, 37; Scholl, *Monatsh.*, 1918, **39**, 238) or, more conveniently, by one-stage synthesis from catechol and *o*-phenylenediamine (Ris, *Ber.*, 1886, **19**, 2206; Hinsberg and Garfunkel, *Annalen*, 1896, **292**, 258). The latter reaction appears to

* Part I, preceding paper.

have confused many authors, who have regarded it either as giving a mixture of phenazine and dihydrophenazine, or as giving phenazine directly. Present experience is that dihydrophenazine is the sole product. This compound may be sublimed unchanged in a vacuum or recrystallised in the absence of air, but it is partly oxidised to phenazine by the usual manipulations in air. The most ready conversion into phenazine was by oxidative sublimation; this method gives pure phenazine in excellent overall yield from *o*-phenylenediamine and it is undoubtedly superior to others which have been used for the preparation of this base (cf. the difficulties encountered by Campbell, Le Fèvre, Le Fèvre, and Turner, *J.*, 1938, 408).

Acylation of dihydrophenazine is complicated by the ready tendency of the base to undergo oxidation in solution. It is true that, by the use of an excess of acetic anhydride alone, either a mono- or a di-acetyl derivative may be prepared, according to conditions (see Kehrmann and Havas, *Ber.*, 1913, **46**, 341; Stscherbina, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 613; Puschkareva and Postovski, *J. Gen. Chem. Russia*, 1938, **8**, 158), but with acid chlorides, or with acetic anhydride in a solvent, careful exclusion of air is necessary. When, for example, dihydrophenazine and acetic anhydride (1 mol. each) are stirred together in acetone in air, blue prisms of phenazhydrin (Clemo and McIlwain, *J.*, 1934, 1991) soon separate. However, by working under carbon dioxide, a true comparison of the reactivity of this base in relation to that of analogous diacidic basis may be made. It is then clear that dihydrophenazine is both less reactive and less inclined to give only disubstituted products than either tetrahydroquinoxaline or *trans*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydrophenazine. Even with a large excess of acetic anhydride, monoacetyldihydrophenazine (I; R = Ac, R′ = H) is the sole product formed at room temperature (in acetone or without a solvent) and the main product after short boiling; conversion into diacetyldihydrophenazine (I; R = R′ = Ac) is only complete after ½ hour's refluxing with an excess of the reagent. Similarly monobenzoyl- and monocarbethoxy-dihydrophenazine were readily prepared by using an excess of the appropriate acid chloride in either acetone or pyridine; no disubstitution occurred in either case when the reactions were conducted at room temperature.

5-Acetyl- (I; R = Ac, R′ = Me), 5-carbethoxy- (I; R = CO_2Et, R′ = Me), and 5-benzoyl-5 : 10-dihydro-10-methylphenazine (I; R = Bz, R′ = Me) were prepared from 5 : 10-dihydro-5-methylphenazine (I; R = Me, R′ = H) by standard methods in an inert atmosphere, but none of these was converted into the corresponding quaternary salts by methyl toluene-*p*-sulphonate or methyl iodide, alone or in various solvents. In each case the starting material was recovered unchanged, or else oxidised to green amorphous products. As in the case of tetrahydroquinoxaline (preceding paper), neither (I; R = R′ = H) nor (I; R = Me, R′ = H) could be induced to react with diethylcarbamyl chloride.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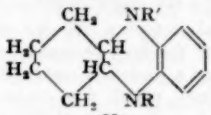
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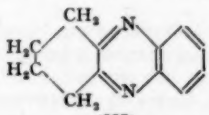
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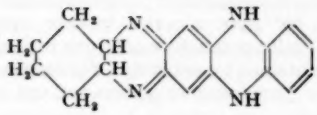
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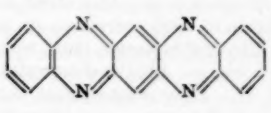
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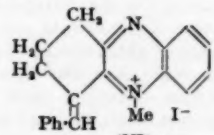
(VI)

trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-Octahydrophenazine (II; R = R′ = H) was prepared by reduction of 1 : 2 : 3 : 4-tetrahydrophenazine (III) (Clemo and McIlwain, *J.*, 1936, 258, 1698) which, in turn, results in 60—70% yield by condensation between *cyclo*hexane-1 : 2-dione and *o*-phenylenediamine in sodium acetate–acetic acid (Clemo and McIlwain, *J.*, 1934, 1991). Two by-products have been isolated in the latter reaction: one, obtained always in less than 1% yield, has been previously isolated and identified as *cis*-

1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydrophenazine *idem, ibid.*; the other, formed in 12—15% yield, is a high-melting base, $C_{18}H_{18}N_4$, which forms a dihydrochloride and a diacetyl derivative. When the known susceptibility of *o*-phenylene-diamines to oxidative attack in the 4 : 5-positions (cf. the oxidation of *o*-phenylenediamine itself to diaminophenazine) is borne in mind, and also the experimental evidence for an oxidative process in the reaction (in the isolation of an octahydrophenazine), (IV) seemed a possible structure. Dehydrogenation to the parent quinoxalinophenazine (V) (Dutt, *J.*, 1926, 1180; see, however, Badger and Pettit, *J.*, 1951, 3211) could not, however, be accomplished; the structure of the base therefore remains in doubt pending synthetic approaches which are in progress.

In reactivity towards acylating agents, the octahydrophenazine was intermediate between 1 : 2 : 3 : 4-tetrahydroquinoxaline and 5 : 10-dihydrophenazine. For example, when each base is treated with a 9-molar excess of acetic anhydride in acetone (48 hours at room temperature), tetrahydroquinoxaline gives only diacetyltetrahydroquinoxaline, dihydrophenazine gives only monoacetyldihydrophenazine, whilst the octahydrophenazine gives a mixture of its monoacetyl (II; R = Ac, R′ = H) (30%) and diacetyl (II; R = R′ = Ac) (54%) derivatives. Other examples may be found in the Experimental section. On the other hand there is a tendency towards disubstitution (particularly when acid chlorides are used) which is equal to that shown by tetrahydroquinoxaline. Indeed only 5 : 10-dicarbethoxy-*trans*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydrophenazine (II; R = R′ = CO_2Et) could at first be isolated by reaction between equimolar proportions of the base and chloroformic ester in various solvents. When, later, the importance of pH was disclosed in the tetrahydroquinoxaline series (Part I, preceding paper), analogy suggested that the failure to isolate monocarbethoxyoctahydrophenazine might be due to a relatively low reaction pH (because of hydrogen chloride liberated from the chloroformic ester during reaction and hydrolysis). In conformity, at a controlled pH of 7, 5-carbethoxy-*trans*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydrophenazine was the exclusive product. At pH 3, only the dicarbethoxy-derivative was formed. Mono- and di-benzoyloctahydrophenazine were prepared likewise. Since the pK_a values of the octahydrophenazine and its monoacyl derivatives correspond approximately with those of tetrahydroquinoxaline (see Part I), these results lend additional support to the arguments advanced in Part I.

Since 1 : 2 : 3 : 4-tetrahydrophenazine (III) may be regarded as a 2 : 3-dialkylquinoxaline, the methylene groups in the 1 and 4 positions were expected to be reactive; condensation between the corresponding methiodide and *p*-dimethylaminobenzaldehyde readily took place, yielding the deep blue cyanine-like compound (VI).

Experimental

M. p.s are uncorrected.

5 : 10-*Dihydrophenazine*.—Commercial catechol (25 g.) and *o*-phenylenediamine (24 g.) were heated in a sealed tube at 200—210° for 35—40 hours; the product was digested rapidly with water at 60° (400 ml. in all), giving a greenish residue of crude 5 : 10-dihydrophenazine (33 g., 82% based on *o*-phenylenediamine), which was dried over solid sodium hydroxide *in vacuo* and stored under dry carbon dioxide. Portions of this material were purified as required (usually in 5-g. batches) by dissolution in cold acetone and filtration (charcoal); partial evaporation of the filtrate and addition of light petroleum (b. p. 40—60°) gave colourless leaflets (with a slight green sheen) of pure dihydrophenazine (80% recovery) (all operations under dry carbon dioxide), m. p. 280° (decomp.; vac.). Identical material was obtained by reduction of phenazine (Claus, *Annalen*, 1873, **168**, 8). Dihydrophenazine sublimes unchanged in a vacuum and is almost insoluble in air-free alcohol, benzene, and chloroform.

Phenazine.—For sublimation, the crude dihydrophenazine (33 g.), obtained as above, was placed in a 250-ml. wide-armed retort fitted with an oxygen lead, and contained in an air-oven so that ¾ of the arm of the retort projected out of the oven. A slow stream of dry oxygen was then passed through the retort and the temperature was raised to 210—220°. Almost pure phenazine (22·1 g., 55% based on *o*-phenylenediamine), m. p. 169—170°, sublimed into the side-arm during 5—7 hours. Recrystallisation from ethanol (*ca.* 250 ml.) gave massive, yellow prismatic needles (20·3 g.) of pure phenazine, m. p. 171—172°.

Acetylation of 5 : 10-*Dihydrophenazine*.—(*a*) Dihydrophenazine (0·25 g.) was dissolved in

acetone (7·5 ml.) under dry carbon dioxide, acetic anhydride (1·4 ml., 10 mols.) added, and the solution left stoppered under carbon dioxide at room temperature for 48 hours. 5-Acetyl-5 : 10-dihydrophenazine (0·2 g.), m. p. 253—254° (decomp.), was isolated by filtration, and a further crop (40 mg.) by evaporation of the filtrate; recrystallisation from acetone gave snow-white cubes, m. p. 254—255° (decomp.) (Tichwinski and Wolochowitsch, *J. Russ. Phys. Chem. Soc.*, 1905, **37**, 8, and Stscherbina, *loc. cit.*, give m. p. 255°; Puschkareva and Postovski, *loc. cit.*, give m. p. 153·5—154°) (Found: C, 74·9; H, 5·3, N, 12·3. Calc. for $C_{14}H_{12}ON_2$: C, 75·0; H, 5·4; N, 12·5%). When equimolar quantities of the reactants were used under otherwise identical conditions, 60% of the dihydrophenazine was recovered unchanged.

(*b*) Dihydrophenazine (0·5 g.) and acetic anhydride (5 ml.) were boiled gently for a few seconds until solution occurred; colourless prismatic needles of the above monoacetyldihydrophenazine (0·51 g.), m. p. 254—255° (decomp.), separated on cooling, which were isolated by filtration followed by washing with ether. The same product was obtained after a paste of dihydrophenazine (1 mol.) and acetic anhydride (2 mols.) had been left at room temperature for 2 days, or a suspension of these reactants had been warmed in acetic acid (3 parts by vol.) for 5 minutes at 95°.

(*c*) When dihydrophenazine (0·5 g.) or monoacetyldihydrophenazine (0·5 g.) and acetic anhydride (5 ml.) were heated gently under reflux for ½ hour or 3 hours, the sole product (0·62 g.) was 5 : 10-diacetyl-5 : 10-dihydrophenazine, which separated in colourless prisms, m. p. 179—180° (165—170° on admixture with monoacetyldihydrophenazine), after decomposition of the excess of anhydride with hot water (20 ml.); this was very appreciably more soluble than the monoacetyl compound in alcohol, acetic acid, or acetone.

Phenazhydrin.—When acetic anhydride (0·28 ml.) was stirred into a solution of dihydrophenazine (0·5 g.) in acetone (15 ml.) in the presence of air, blue prisms of phenazhydrin (0·25 g.), m. p. 225° (decomp.), separated after 1 hour, which could be recrystallised from ethanol without change in m. p. (Found: C, 79·7; H, 4·8; N, 15·3. Calc. for $C_{12}H_8N_2$,$C_{12}H_{10}N_2$: C, 79·55; H, 5·0; N, 15·45%). A specimen prepared by mixing of solutions of dihydrophenazine (0·1 g.) and phenazine (0·1 g.) in acetone was a darker blue and had m. p. 210° (decomp.) [Clemo and McIlwain, *J.*, 1934, 1991, give m. p. 209° (decomp.); Schlenk and Bergmann, *Annalen*, 1928, **463**, 306, give m. p. 224—226°]; there was, however, no depression in m. p. on admixture, and the two specimens were otherwise identical. (The existence of two forms of phenazhydrin has been discussed by Dufraise, Étienne, and Toromanoff, *Compt. rend.*, 1951, **232**, 2379.) Both specimens (100 mg.), when dissolved in hot benzene (10 ml.) and quickly cooled, gave colourless crystals of dihydrophenazine (30 mg.) (identified by m. p. and mixed m. p. determinations, and by conversion into monoacetyldihydrophenazine); evaporation of the filtrate and addition of light petroleum (b. p. 40—60°) gave yellow needles (55 mg.) of phenazine, m. p. and mixed m. p. 170—171°.

Monobenzoyl- and *Monocarbethoxy-dihydrophenazine.*—These compounds were the sole products isolated from the reaction between dihydrophenazine and an equivalent or excess of the appropriate acid chloride in acetone or pyridine at room temperature (all reactions under dry carbon dioxide). For comparative purposes, the following details of the cases involving equimolar proportions of reactants are given. (*a*) Air-free acetone (15 ml.), dihydrophenazine (0·5 g.), and freshly distilled benzoyl chloride (0·32 ml.) were left under carbon dioxide for 3 days. The solid, which separated, was digested with hot acetone (20 ml. in all), and the digests (after filtration in the cold) were then evaporated, yielding *5-benzoyl-5 : 10-dihydrophenazine* (0·13 g.), after crystallisation from acetone–light petroleum (charcoal); this formed soft, colourless plates from benzene, or colourless prismatic needles from aqueous acetone; both forms had m. p. 224—225° (Found: N, 9·8. $C_{19}H_{14}ON_2$ requires N, 9·8%). A further crop (0·27 g.; total yield, 51%) was obtained from the original mother-liquors. Chloroformic ester (0·25 ml.) and a reaction time of 16 hours gave *5-carbethoxy-5 : 10-dihydrophenazine* (0·12 g., 17%) (isolated by dilution with water, basification, and extraction with benzene), which separated from light petroleum (b. p. 40—60°) containing a little ethanol or acetone (very long solubility lag) in pale yellow prisms, m. p. 109—110° (Found: N, 10·9. $C_{15}H_{14}O_2N_2$ requires, N, 11·0%). (*b*) Specimens identical in m. p. and mixed m. p. with the above were obtained when pyridine (5 ml.), dihydrophenazine (0·25 g.), and benzoyl chloride (0·16 ml.) or chloroformic ester (0·25 ml.) were left under carbon dioxide for 24 hours. The yield of crude benzoyl derivative, which separated on dilution with water (20 ml.), was 0·15 g. (38%); the carbethoxy-derivative (yield 66%) was similarly obtained as an oil, which solidified during a week at room temperature.

5 : 10-*Dihydro-5-methylphenazine.*—A solution of pure phenazine (5 g.) in nitrobenzene (25 ml.) was heated at the b. p. for a few seconds in order to expel traces of moisture, the solution

allowed to cool to 120°, and methyl sulphate (3·8 ml.) added with stirring. After 15 minutes at 100—110°, the suspension was cooled, diluted to 250 ml. with dry ether, and filtered; after washing of the residue with dry ether, almost pure methyl 5-methylphenazonium sulphate (6·1 g.) was obtained, which was used without further purification. Recrystallisation from 80% aqueous ethanol–ether gave glittering, yellow-brown needles; their m. p. (rapid heating) 198° (decomp.) varied according to the rate of heating. A solution of this salt (3 g.) in 3N-hydrochloric acid (150 ml.), containing a trace of platinum chloride, was stirred under benzene (100 ml.), carbon dioxide was bubbled into the solution, and zinc dust (12 g.) was added in portions. When the aqueous phase was colourless (up to ½ hour; warming may be necessary towards the end of the reaction), the benzene layer was quickly run off and combined with two benzene extracts of the aqueous phase. After washing with water, drying (K_2CO_3), evaporation and addition of light petroleum (b. p. 60—80°) (all operations under dry carbon dioxide), 5 : 10-dihydro-5-methylphenazine separated in colourless needles (1·6—2·0 g.), m. p. 163—164° (vac.) (Hantzsch, *Ber.*, 1916, **49**, 511, gives m. p. 164° under carbon dioxide). Treatment with benzoyl chloride or chloroformic ester in pyridine (16 hours at room temperature under carbon dioxide) gave *5-benzoyl-5 : 10-dihydro-10-methylphenazine* (crude yield, 80%; prisms from aqueous acetic acid, which retained a yellow-green colour after repeated recrystallisation), m. p. 164—165° (Found: C, 78·8; H, 5·45; N, 9·9. $C_{20}H_{16}ON_2$ requires C, 80·0; H, 5·4; N, 9·3%), and *5-carbethoxy-5 : 10-dihydro-10-methylphenazine* (crude yield, 90%; colourless needles from aqueous acetic acid), m. p. 84—85° (Found: C, 71·5; H, 6·09; N, 10·8. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0; N, 10·45%).

1 : 2 : 3 : 4-*Tetrahydrophenazine.*—*cyclo*Hexane-1 : 2-dione (10·5 g.), *o*-phenylenediamine (11 g.), freshly fused sodium acetate (15 g.), and glacial acetic acid (45 ml.) were heated under reflux for 2 hours. The hot solution was then poured into water (250 ml.), giving crude 1 : 2 : 3 : 4-tetrahydrophenazine (11·5 g., 67%), m. p. 88—90°, which separated from light petroleum (b. p. 40—60°) in almost colourless prisms, m. p. 92—93° (Clemo and McIlwain, *J.*, 1934, 1991, give m. p. 92·5°). Basification of the mother-liquors (aqueous ammonia) gave a gum, which yielded a granular *base* (? IV) (2·15 g.) when digested with acetone (100 ml.) (digests A). For purification, this, and a further crop (1·4 g.), which separated slowly on addition of excess of 20% aqueous sodium hydroxide to the basified mother-liquors, were first converted into the corresponding *dihydrochloride* (colourless needles from dilute hydrochloric acid or aqueous acetone), m. p. 320—322° (decomp.), by recrystallisation from 4N-hydrochloric acid (Found: C, 54·05; H, 6·0; N, 14·1; Cl, 18·0. $C_{18}H_{18}N_4,2HCl,2H_2O$ requires C, 54·15; H, 6·1; N, 14·0; Cl, 17·8%). The regenerated base separated from aqueous ethanol in small, colourless prisms, m. p. 264—265° [Found: C, 74·5; H, 6·1; N, 19·15%; *M* (ebullioscopic in ethanol), 290. $C_{18}H_{18}N_4$ requires C, 74·45; H, 6·25; N, 19·3%; *M*, 290], which yielded a *diacetyl* derivative (clusters of small, colourless needles from pyridine), m. p. 245—247° (decomp.), with boiling acetic anhydride (5 parts by volume), alone or in ethanol (Found: C, 70·75; H, 5·5; N, 14·85. $C_{22}H_{22}O_2N_2$ requires C, 70·6; H, 5·9; N, 14·95%). *cis*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-Octahydrophenazine (0·1 g.), m. p. 146—147° alone and on admixture with an authentic specimen (Clemo and McIlwain, *J.*, 1936, 1698), was obtained from the acetone digests A by evaporation and recrystallisation of the residual oil from light petroleum (b. p. 40—60°).

Dehydrogenation Experiments.—Tetrahydrophenazine was recovered unchanged after prolonged heating under reflux in sulphur-free xylene with Raney nickel (cf. Badcock and Pausacker, *J.*, 1951, 1373); no useful product was obtained after 2 hours' refluxing in xylene with chloranil. On the other hand, phenazine was formed in quantitative yield when a mixture of the tetrahydrophenazine or *cis*- or *trans*-octahydrophenazine was heated with 30% palladium–charcoal (Baker, McOmie, and Norman, *J.*, 1951, 1117) for ½ hour at 245—250°. Under similar conditions the base, m. p. 264—265°, was unchanged; even after prolonged heating at temperatures ranging from 230° to 300° the loss of hydrogen corresponded to less than 4 atoms per mole of base.

Reactions of Tetrahydrophenazine Methiodide.—(*a*) When the methiodide (0·8 g.) (McIlwain, *J.*, 1937, 1701) in cold pyridine (3 ml.) was treated with *p*-dimethylaminobenzaldehyde (0·4 g.) in acetic anhydride (3 ml.), the colour, initially red, rapidly became green and within 2 minutes was a very deep blue; 1-p-*dimethylaminobenzylidene*-1 : 2 : 3 : 4-*tetrahydrophenazine methiodide* (1·0 g.), which was precipitated by addition of dry ether, formed small, deep maroon-coloured needles, m. p. (variable) 160—180° (decomp.) after marked previous sintering, from ethanol–ether; this gave intense blue colours to water, ethanol, or acetic acid, destroyed by addition of mineral acids (Found: C, 58·4; H, 5·4; N, 9·15. $C_{22}H_{24}N_3I$ requires C, 57·8; H, 5·3; N, 9·2%).

(*b*) The methiodide yielded the dehydro-base (McIlwain, *loc. cit.*), b. p. 169—170°/1 mm., on basification, but neither compound gave a useful product after reduction with sodium in boiling ethanol.

trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*Octahydrophenazine*.—Sodium (20 g.) was added gradually to a gently refluxing solution of crude tetrahydrophenazine (3·6 g.) in absolute ethanol (150 ml.). When all the sodium had reacted, the now colourless solution was decanted into water (300 ml.), and the precipitate of crude octahydrophenazine (2·8—3·0 g.) collected and washed with water. The products from four such runs were dissolved in hot ethanol (100—150 ml.) and concentrated hydrochloric acid added; the *monohydrochloride*, which separated on cooling, formed colourless prisms, m. p. 315° (decomp.), when recrystallised from water under nitrogen (in the presence of air, the crystals become pink) (Found: C, 63·7; H, 7·6; N, 12·5. $C_{12}H_{16}N_2$,HCl requires C, 64·1; H, 7·6; N, 12·5%); it gave the pure base (10·5—11·5 g., 71—78%), m. p. 155—156° (Clemo and McIlwain, *J.*, 1936, 258, give m. p. 156°), on neutralisation with aqueous ammonia. The hydrochloride was only sparingly soluble in ethanol.

Acetylation.—(*a*) A solution of the above octahydrophenazine (0·5 g.) and acetic anhydride (2·8 ml., 10 mols.) in acetone (15 ml.) was set aside at room temperature for 48 hours (unchanged octahydrophenazine was present after 24 hours). Addition of dry ether saturated with hydrogen chloride then gave 5-*acetyl*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine hydrochloride* (0·21 g., 30%), which formed soft, colourless needles, m. p. 292—294° (decomp.), from dry ethanol–ether, easily soluble in warm ethanol (cf. octahydrophenazine hydrochloride) (Found: C, 62·7; H, 7·05; N, 11·0. $C_{14}H_{18}ON_2$,HCl requires C, 63·0; H, 7·17; N, 10·5%); the corresponding *base* separated from light petroleum (b. p. 40—60°) in rosettes of colourless needles, m. p. 118—119° (Found: C, 72·95; H, 7·7; N, 12·2. $C_{14}H_{18}ON_2$ requires C, 73·0; H, 7·9; N, 12·2%). The original mother-liquors were basified (dilute aqueous ammonia), and the organic layer separated, combined with two ether-extracts of the aqueous layer, dried, and evaporated, giving 5 : 10-*diacetyl*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine* (0·39 g., 54%), which formed colourless prisms, m. p. 175—176°, when recrystallised from acetone–light petroleum (Found: C, 70·75; H, 6·6; N, 10·7. $C_{16}H_{20}O_2N_2$ requires C, 70·55; H, 7·4; N, 10·3%).

(*b*) The octahydrophenazine (2 g.), dissolved in ethanol, (50 ml.) was treated with stirring at 45—50° with acetic anhydride (2·2 ml., equiv. to 2 mols.), added dropwise during 5 minutes. After 1½ hours at this temperature, the solution was diluted with water (100 ml.), then basified (aqueous ammonia), and the unchanged octahydrophenazine (0·84 g., 42%) collected by filtration; only monoacetyloctahydrophenazine, m. p. 118—119°, alone and on admixture with the above specimen, remained in the filtrate, from which it was isolated *via* the hydrochloride (1·1 g., 39%) obtained by ether-extraction, evaporation of the extracts, and addition of dry ethereal hydrogen chloride to a solution of the residue in acetone.

(*c*) Diacetyloctahydrophenazine, m. p. 175—176°, was the sole product obtained after dissolution of octahydrophenazine (0·3 g.) in warm acetic anhydride (2 ml.) followed by immediate cooling, or after refluxing of the reactants for 2 hours.

Carbethoxylation and Benzoylation at Controlled pH.—(*a*) Equimolar proportions of chloroformic ester (0·51 ml.) and octahydrophenazine (1 g.) were allowed to react at pH 7 under conditions described in Part I (preceding paper) except for the omission of buffering; by substitution of water (100 ml.), in place of the buffer solution, the pH could be controlled within ±0·2 unit, as against ±0·02 unit when a buffer is used. Reaction was less rapid than in the case of tetrahydroquinoxaline, as shown by the longer time required for the pH to reach equilibrium and by appreciable hydrolysis of the acid chloride. When, finally, there was no tendency for the pH to fall, the alcohol was partly removed on the steam-bath under reduced pressure, then the solution was cooled, made acid to Congo-red with hydrochloric acid, and extracted with ether. Evaporation of the dried extracts, followed by addition of dry ether saturated with hydrogen chloride to a solution of the residue in dry acetone (10 ml.), gave, slowly, 5-*carbethoxy*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine hydrochloride* (0·5 g., 32%), which formed colourless clusters of needles, m. p. 228—230° (slight decomp.), from dry ethanol–ether (Found: N, 9·45. $C_{15}H_{20}O_2N_2$,HCl requires N, 9·4%); the dicarbethoxy-derivative (see below) was not detected in the mother-liquors. On contact with water, this hydrochloride dissociated into the corresponding *base*, which, after drying, separated from light petroleum (b. p. 60—80°) in compact pale brown prisms (almost colourless when pulverised), m. p. 98—99° (Found: C, 69·0; H, 8·0; N, 10·5. $C_{15}H_{20}O_2N_2$ requires C, 69·2; H, 7·75; N, 10·75%). The aqueous phase from the above ether-extraction contained unchanged octahydrophenazine (0·34 g.) isolated by basification (aqueous ammonia) and further evaporation.

In an exactly similar manner, benzoyl chloride (0·55 ml.) and octahydrophenazine (0·9 g.)

gave 5-*benzoyl*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine hydrochloride* (0·35 g., 22%) (colourless needles from ethanol–ether), which melted slowly, with decomp., between 280° and 310°, after marked sintering above 230° (Found: N, 8·5. $C_{19}H_{20}ON_2$,HCl requires N, 8·5%), and the corresponding *base* (pale brown prisms from benzene–light petroleum), m. p. 155—156° (Found: C, 78·2; H, 7·1; N, 9·85. $C_{19}H_{20}ON_2$ requires C, 78·05; H, 6·9; N, 9·6%). The recovery of unchanged octahydrophenazine was 45%, and of benzoyl chloride (as ethyl benzoate) 30—40%.

(*b*) When the above reactions were conducted at pH 3±0·2, the ethereal residues did not yield a hydrochloride, which indicated the absence of monosubstitution; in both cases, recrystallisation of the residue from aqueous acetic acid gave the appropriate, almost pure diacyl derivative. There were so obtained 5 : 10-*dicarbethoxy*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine* (11—15%, based on octahydrophenazine), in colourless needles, m. p. 76—77° (65—70° when mixed with the monocarbethoxy-derivative) (Found: C, 69·95; H, 7·0; N, 8·45. $C_{18}H_{24}O_4N_2$ requires C, 65·05; H, 7·3; N, 8·45%), and the *dibenzoyl* derivative (10—12%) in flesh-coloured needles (prismatic needles from benzene–light petroleum), m. p. 168—169° (131—138° when mixed with the monobenzoyl derivative) (Found: C, 78·9; H, 6·2; N, 6·85. $C_{26}H_{24}O_2N_2$ requires C, 78·8; H, 6·1; N, 7·05%). The recovery of unchanged base was 40—60%. The same products were obtained when equimolar proportions of octahydrophenazine and acid chloride were allowed to react in pyridine, ethanol, or acetone at various temperatures without reference to the pH of the medium, or when excess of the acid chloride was used in pyridine.

Benzenesulphonylation.—(*a*) Benzenesulphonyl chloride (0·34 ml., 1 mol.) was added dropwise to a solution of octahydrophenazine (0·5 g., 1 mol.) in pyridine (5 ml.) at 20—25° (mechanical stirring). After 14 hours at room temperature, the crude product (0·65 g.), obtained by dilution with water (15 ml.), was dissolved in acetone (25 ml.) and treated with dry ether saturated with hydrogen chloride; the hydrochloride (0·68 g., 70%) so precipitated gave 5-*benzenesulphonyl*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine* (0·43 g., 50%) on basification [aqueous ammonia in ethanol (20 ml.) and water (5 ml.)], which formed colourless needles, m. p. 150—151°, from aqueous ethanol or benzene–light petroleum (Found: C, 65·65; H, 6·0; N, 8·6. $C_{18}H_{20}O_2N_2S$ requires C, 65·85; H, 6·1; N, 8·5%).

(*b*) With excess of the acid chloride (4 mols.) the product was 5 : 10-*dibenzenesulphonyl*-trans-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-*octahydrophenazine* (crude yield, 98%), which separated from ethanol in large, colourless, prismatic needles, m. p. 169—170° (or, occasionally, in colourless prisms, m. p. 185—186°) (Found: C, 61·5; H, 5·1; N, 6·1. $C_{24}H_{24}O_4N_2S_2$ requires C, 61·5; H, 5·16; N, 6·0%).

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767. *Studies of Trifluoroacetic Acid. Part VI.* Trifluoroacetyl Derivatives of Amines.*

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A series of trifluoroacetylated amines has been prepared by using trifluoroacetic anhydride. Those derived from primary aromatic amines and from 2 : 2 : 2-trifluoroethylamine may be titrated with aqueous alkali and recovered when the solutions are acidified. Aniline reacts with trifluoroacetic anhydride–acetic acid, and with trifluoroacetic acid–acetic anhydride, to give both the *N*-acetyl and *N*-trifluoroacetyl derivatives. Acetanilide and *N*-cyclohexylbenzamide give diacyl derivatives when treated with trifluoroacetic anhydride.

APART from Swarts's original paper on trifluoroacetic acid (*Bull. Acad. roy. Belg., Classe Sci.*, 1922, **8**, 343) in which he described the amide and the anilide, little has been reported about the chemistry of *N*-trifluoroacetyl derivatives, although a few of these compounds

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have been mentioned briefly in other connections (cf. Park, Englert, and Meek, *J. Amer. Chem. Soc.*, 1951, **73**, 5898; Shine and Niemann, *ibid.*, 1952, **74**, 97; Weygand and Csendes, *Angew. Chem.*, 1952, **64**, 136; Dickey, U.S.P. 2,436,100). We have made certain of these compounds by treatment of amines with trifluoroacetic anhydride, reactions which, as expected, proceeded extremely readily (see Table 1). With an excess of amine (method A) the trifluoroacetate salt (isolated in some cases) was formed as well as the amide; with an excess of anhydride (method B) this salt was itself trifluoroacetylated. That the trifluoroacetyl groups of the products from aromatic amines were in fact carried on the amino-groups and not on the aromatic nuclei was proved by hydrolysis of the amides with dilute alkali and formation of the known *N*-benzoyl derivatives.

Though they were unaffected during 3—4 hours in boiling dry methyl alcohol (cf. the trifluoroacetate esters; Bourne, Tatlow, and Tatlow, *J.*, 1950, 1367), the trifluoroacetylamines were decomposed fairly readily by aqueous alkali (keeping them for an hour with N-sodium hydroxide caused extensive hydrolysis). It was found also that some of them dissolved readily in aqueous alkali and, if the solutions were acidified without long delay, the unchanged amides were reprecipitated. Accordingly, the trifluoroacetylated amines, acetanilide, and 2 : 5-dichloroacetanilide were titrated, in aqueous-alcoholic solution, against approx. 0·1N-sodium hydroxide. The two acetylated amines, the trifluoroacetylated secondary amines, *N-cyclo*hexyltrifluoroacetamide, and *N*-benzyltrifluoroacetamide did not take up alkali under these conditions, whereas the trifluoroacetylated primary aromatic amines and *N*-(2 : 2 : 2-trifluoroethyl)trifluoroacetamide did (end-points *ca.* pH 11—11·5); the equivalents thus determined showed these amides to be monobasic (see Table 2). Acidification of each solution regenerated the amide, showing that the alkali take-up was due to the formation of a sodio-derivative and was not caused by hydrolysis.

It is evident that the strongly electrophilic trifluoromethyl group is primarily responsible for this display of acidity by the amido-function because, although analogous acetyl compounds give sodio-derivatives with metallic sodium in inert solvents (see, for example, Hepp, *Ber.*, 1877, **10**, 327), they do not in general give them with aqueous bases. Further, in order to be acidic the substituted trifluoroacetamide must have an amine component which possesses a suitable electrophilic residue (*e.g.*, a phenyl or trifluoroethyl group). It is also of interest that the amides containing aromatic nuclei become progressively more acidic, as indicated by the steeper slopes at the end-points of the titration curves, with increasing electrophilic character of the nuclear substituents; in this way a general method might be developed for comparison of the basic strengths of weak amines.

That the trifluoroethyl group has a profound influence on the reactions of the amino-group in 2 : 2 : 2-trifluoroethylamine has been demonstrated previously, for with nitrous acid, the amine gives 2 : 2 : 2-trifluorodiazoethane (Gilman and Jones, *J. Amer. Chem. Soc.*, 1943, **65**, 1458). Our sample of trifluoroethylamine was prepared in good yield by reduction of trifluoroacetamide with lithium aluminium hydride. Previous methods have involved reduction of the nitrile (Gilman and Jones, *loc. cit.*) or treatment of 1-chloro-2 : 2 : 2-trifluoroethane with ammonia (Benning and Park, U.S.P. 2,348,321).

Sulphonamides derived from primary amines have long been known to be alkali-soluble (Hinsberg, *Ber.*, 1890, **23**, 2962), though, unlike the trifluoroacetamides, they are hydrolysed by alkali only with difficulty (cf. Schreiber and Shriner, *J. Amer. Chem. Soc.*, 1934, **56**, 114).

Recent work in this department has shown that trifluoroacetic anhydride promotes reactions between carboxylic acids and hydroxy-compounds or activated aromatic compounds (Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2976; 1951, 718). Accordingly, it was of interest to examine the reactions of such anhydride–acid mixtures with amines; the reactions were found, however, to be more complex in this case. Aniline, treated with an excess of an equimolecular mixture of acetic acid and trifluoroacetic anhydride, gave roughly equal proportions of acetanilide and of trifluoroacetanilide, and excess of aniline treated with the mixture in carbon tetrachloride solution gave more of the trifluoroacetyl derivative. With acetic anhydride–trifluoroacetic acid both products were again given; by use of a mixture of benzoic acid and trifluoroacetic anhydride, benzanilide and trifluoroacetanilide were obtained. The separation of the anilide mixtures into pure

components was difficult, even by utilisation of the preferential solubility of the trifluoro-derivative in alkali, so that the yields recorded are probably low. With aniline trifluoroacetate, trifluoroacetic anhydride gave trifluoroacetanilide, acetic anhydride gave acetanilide, and a mixture of acetic acid and trifluoroacetic anhydride gave the trifluoroacetyl derivative, all in good yield.

The mechanism suggested for the reactions of acetic acid–trifluoroacetic anhydride (Bourne, Randles, Tatlow, and Tedder, *Nature*, 1951, **168**, 942) involved the formation of the unsymmetric anhydride, $CF_3{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3$, which can be formed also from mixtures of trifluoroacetic acid and acetic anhydride. This unsymmetric anhydride would be expected to react, if in the molecular form, to give trifluoroacetyl derivatives preferentially [compare Emery and Gold (*J.*, 1950, 1443, 1447, 1455) for reactions of unsymmetric anhydrides of acetic and chloroacetic acids]. However, conductivity measurements suggest that ionization of the unsymmetric anhydride occurs to a small extent to give $CH_3{\cdot}CO^+$ and $CF_3{\cdot}CO_2^-$, and that it is the acetylium cation which reacts preferentially with hydroxy-compounds and activated aromatic compounds (Bourne, Randles, Tatlow, and Tedder, *loc. cit.*). On the other hand, the acetyl and trifluoroacetyl derivatives which are formed from amines with acetic anhydride–trifluoroacetic acid and acetic acid–trifluoroacetic anhydride would seem to arise mainly from the unsymmetric anhydride in its molecular form. The probable reason for this is that the basicity of the amine suppresses the slight ionization of the unsymmetric anhydride; for example, the addition of a base to acetic acid–trifluoroacetic anhydride (*i.e.*, $CF_3{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3 + CF_3{\cdot}CO_2H$) would, by a proton transfer, rapidly produce a considerable concentration of $CF_3{\cdot}CO_2^-$ ions, thus greatly reducing the concentration of the $CH_3{\cdot}CO^+$ cations. The same result would occur if the unsymmetric anhydride reacted with $CF_3{\cdot}CO_2^-$ ions to give $CH_3{\cdot}CO_2^-$ ions and $(CF_3{\cdot}CO)_2O$. Further, molecular anhydrides appear to acylate amines more rapidly than hydroxy-compounds and these factors together would mean that the molecular unsymmetric anhydride should play an important part in the reaction with amines. Thus, these considerations lead to the conclusion that, in accordance with experimental results, a mixture of anilides, with the trifluoroacetylated product predominating, would be expected. It is significant that the treatment of aniline trifluoroacetate with acetic acid–trifluoroacetic anhydride gave a good yield of trifluoroacetanilide, no acetanilide being isolated.

Acetanilide and *N-cyclo*hexylbenzamide formed *N*-acetyl-*N*-trifluoroacetylaniline and *N*-benzoyl-*N*-trifluoroacetyl*cyclo*hexylamine, respectively, when treated with trifluoroacetic anhydride. These diacyl products were very readily hydrolysed and were susceptible also to methanolysis, the trifluoroacetyl residue being removed in each case, leaving the original acylated amine. *N*-Acetyl-*N*-trifluoroacetylaniline reacted with 2 : 5-dichloroaniline to give 2 : 5-dichlorotrifluoroacetanilide and acetanilide. Infra-red measurements of the trifluoroacetylated benzamide and acetamide derivative, carried out in collaboration with Dr. D. H. Whiffen, suggested that they did, in fact, contain two acyl groups as such [cf. Hunter and Reynolds (*J.*, 1950, 2857) who found no evidence for the existence of imidol forms in various diacyl types]. Diacyl derivatives could not be isolated when trifluoroacetanilide was treated with acetic anhydride, trifluoroacetic anhydride, or acetic acid–trifluoroacetic anhydride, or when benzanilide was treated with trifluoroacetic anhydride, though in the last case there were indications that a very unstable product may have been formed. It appears that the formation of diacyl derivatives from substituted amides is rendered progressively more difficult by the presence of increasingly electrophilic substituents.

At present, the evidence suggests that trifluoroacetic anhydride will be less useful for promoting *N*-acylation by carboxylic acids than it is for effecting *O*-acylation. It may be possible, however, in certain cases to arrange that a significant amount of *N*-acylation does occur, and thus to promote, for example, peptide synthesis.

Experimental

Trifluoroacetylation of Amines.—(*a*) *General methods.* (A) A solution of trifluoroacetic anhydride (1 mol.) in about twice its volume of a dry inert solvent was added at 0° to a solution of the amine (2 mol.) in the minimum volume of the same solvent. After 10—60 minutes, the

volatile matter was removed by distillation under diminished pressure, ice-water was added to the residue, and the precipitated amide was collected and recrystallised.

(B) The amine (1 mol.) was treated with trifluoroacetic anhydride (1—6 mols.) and, after being warmed if necessary to effect solution and then kept for 10—60 minutes, the mixture was

TABLE 1. *Trifluoroacetylation of amines.*

No.	Parent	Amine (g.)	$(CF_3·CO)_2O$ (g.)	Solvent used	Method	Yield (g.)	Solvent for recrystn.*	M. p.
I	NH_2Ph	12·02	13·4	Et_2O	A	7·37	EtOH–H_2O	88·5—90°
		0·66	4·5	CCl_4	B	1·24	Pet B	89—90
II	2 : 5 : 1-$C_6H_3Cl_2·NH_2$	2·35	1·5	Et_2O	A	0·71	EtOH–H_2O	67—68
		0·51	1·2	None	B	0·71	Pet A	67—68·5
III	*p*-$C_6H_4Cl·NH_2$	10·00	8·5	Et_2O	A	6·00	EtOH–H_2O	123—124·5
IV	*p*-$NO_2·C_6H_4·NH_2$	0·49	4·5	Et_2O	B	0·71	,,	151·5—153
V	$[CH_2]_5>CH·NH_2$	1·43	1·5	Et_2O	A	0·62	,,	93—95
		5·00	10·4	Et_2O	B	7·82	Pet C	94—95
VI	*p*-$C_6H_4Me·NH_2$	1·65	1·5	Et_2O	A	1·01	,,	111—112
VII	$CH_2Ph·NH_2$	1·96	3·9	Et_2O	B	2·75	,,	73·5—75
VIII	NHPhMe	1·95	2·1	Et_2O	A	1·32	Pet A	26—27
IX	*p*-MeO·$C_6H_4·NH_2$	9·99	8·6	$CHCl_3$	A	4·84	Pet C	112·5—115
X	*p*-EtO·$C_6H_4·NH_2$	1·97	1·5	Et_2O	A	0·75	,,	141—143
XI	β-$C_{10}H_7·NH_2$	2·07	1·5	Et_2O	A	1·05	,,	146—148
XII	$NHPh_2$	2·44	1·5	Et_2O	A	0·90	EtOH–H_2O	71—72
		0·51	3·7	None	B	0·73	,,	71—72
XIII	*p*-Ph·N:N·$C_6H_4·NH_2$	0·51	3·0	Et_2O	B	0·53	Pet C	176—178

* Pet = light petroleum, b. p. (A) 40—60°, (B) 60—80°, (C) 80—100°.

		Required, %			Found, %		
No.	Formula	C	H	F	C	H	F
I	$C_8H_6ONF_3$	50·8	3·2	30·1	50·8	3·2	30·0
II	$C_8H_4ONCl_2F_3$	37·2	1·6	22·1	36·9	1·5	22·1
III	$C_8H_5ONClF_3$	43·0	2·3	—	43·1	2·4	—
IV	$C_8H_5O_3N_2F_3$	41·0	2·2	24·3	40·8	1·9	23·8
V	$C_8H_{12}ONF_3$	49·2	6·2	29·2	49·6	6·2	29·6
VI	$C_9H_8ONF_3$	53·2	4·0	—	53·0	3·9	—
VII	$C_9H_8ONF_3$	53·2	4·0	28·1	53·4	3·8	28·2
VIII	$C_9H_8ONF_3$	53·2	4·0	—	53·1	3·8	—
IX	$C_9H_8O_2NF_3$	49·3	3·7	—	49·1	3·7	—
X	$C_{10}H_{10}O_2NF_3$	51·5	4·3	—	51·4	4·2	—
XI	$C_{12}H_8ONF_3$	60·3	3·4	—	60·6	3·3	—
XII	$C_{14}H_{10}ONF_3$	63·4	3·8	—	63·0	3·9	—
XIII	$C_{14}H_{10}ON_2F_3$	57·3	3·4	19·4	57·2	3·2	19·2

evaporated under diminished pressure, several portions of carbon tetrachloride being added successively to, and distilled under diminished pressure from, the residue before it was recrystallised.

Details of the trifluoroacetylated amines which were prepared are given in Table 1. Swarts (*loc. cit.*) reported m. p. 87·6° for trifluoroacetanilide; the other *amides* are new.

(*b*) *Trifluoroacetanilide from aniline hydrochloride.* Aniline hydrochloride (0·59 g.) and the anhydride (4·5 g.), treated as in method B, gave trifluoroacetanilide (0·68 g.).

(*c*) *N-(2 : 2 : 2-Trifluoroethyl)trifluoroacetamide.* 2 : 2 : 2-Trifluoroethylamine hydrochloride (1·16 g.) and trifluoroacetic anhydride (7·5 g.) were warmed at 50° for 30 minutes, and the mixture was then distilled under diminished pressure with ether (4 × 10 c.c.) and carbon tetrachloride (10 c.c.). The residual *amide* (XIV) (1·16 g.) had m. p. 51—52°, unchanged by recrystallisation (Found: C, 24·6; H, 1·5; F, 57·9. $C_4H_3ONF_6$ requires C, 24·6; H, 1·55; F, 58·45%). This amide is appreciably volatile, and unless care is taken handling losses are serious.

TABLE 2.

Compound no.		I	II	III	IV	VI	IX	X	XI	XIII	XIV
Equiv. :	Found	192	256	224	227	212	224	240	241	289	196
	Reqd.	189	258	224	234	203	219	233	239	293	195

Potentiometric Titrations of N-Trifluoroacetylated Amines.—Aqueous-alcoholic solutions of the amides (0·1—0·2 g.) were titrated against standard sodium hydroxide solution (*ca.* 0·1N), a Cambridge instrument being used to measure pH. In Table 2 are recorded the equivalents calculated from the titration curves for those amides which are acidic. The curves for acet-

anilide, 2 : 5-dichloroacetanilide, *N-cyclo*hexyltrifluoroacetamide, and *N*-benzyltrifluoroacetamide showed the complete absence of acidic groupings.

After each titration, the solution was acidified with dilute hydrochloric acid, and then extracted with chloroform. The original trifluoroacetylated amines were regenerated (recovery 80—95%), except that recovery of *p*-nitrotrifluoroacetanilide in good yield was difficult owing to rapid hydrolysis at the end-point of the titration.

Reactions of Aniline with Acetic–Trifluoroacetic Acid–Anhydride Mixtures.—(*a*) A mixture of acetic acid (1·89 g., 6·0 mols.) and trifluoroacetic anhydride (6·70 g., 6·0 mols.) was added to aniline (0·49 g., 1·0 mol.), a vigorous reaction ensuing. After 15 minutes at 15°, the volatile constituents were distilled off *in vacuo* with several portions of carbon tetrachloride. A solution of the residue in chloroform was washed with 2N-sodium hydroxide and then with water, dried ($MgSO_4$), filtered, and distilled, to give a residue which, on recrystallisation from light petroleum (b. p. 100—120°), afforded acetanilide (0·155 g., 0·22 mol.), m. p. and mixed m. p. 114—115°. Acidification of the cooled alkaline extract gave trifluoroacetanilide (0·20 g., 0·20 mol.), m. p. and mixed m. p. 88—89°.

(*b*) Aniline (1·48 g., 3·0 mols.) in carbon tetrachloride (27 c.c.), was treated with a mixture of acetic acid (0·32 g., 1·0 mol.), trifluoroacetic anhydride (1·12 g., 1·0 mol.), and carbon tetrachloride (4 c.c.). After 5 minutes' refluxing, the precipitated aniline trifluoroacetate (1·52 g., 1·37 mols.), m. p. 124°, was collected. The solution was evaporated and the residue recrystallised from light petroleum (b. p. 60—80°) and then from aqueous alcohol, to give trifluoroacetanilide (0·488 g., 0·48 mol.); from the mother-liquors acetanilide (0·065 g., 0·09 mol.) was obtained.

(*c*) A mixture of trifluoroacetic acid (1·35 g., 2·2 mols.) and acetic anhydride (0·54 g., 1·0 mol.) was added to aniline (0·49 g., 1·0 mol.). Treatment as in (*a*) gave trifluoroacetanilide (0·119 g., 0·12 mol.) and acetanilide (0·273 g., 0·38 mol.). A similar reaction using aniline (1·0 mol.), acetic anhydride (2·0 mols.), and trifluoroacetic acid (4·0 mols.) gave acetanilide (0·29 mol.) and trifluoroacetanilide (0·33 mol.).

Acylations of Aniline Trifluoroacetate.—(*a*) The salt, treated with trifluoroacetic anhydride, as in method B (p. 4017), gave trifluoroacetanilide (85%).

(*b*) With acetic anhydride, the salt, in a similar process, gave acetanilide in 78% yield.

(*c*) The salt (1·11 g., 1 mol.), treated with a mixture of acetic acid (0·63 g., 2 mols.) and trifluoroacetic anhydride (2·2 g., 2 mols.), afforded trifluoroacetanilide (0·84 g., 83%).

Trifluoroacetylation of Aniline Acetate.—This salt, when treated with trifluoroacetic anhydride, gave trifluoroacetanilide in 68% yield.

N-*Acetyl*-N-*trifluoroacetylaniline.*—(a) *Preparation.* Trifluoroacetic anhydride (2·8 g.) and acetanilide (1·53 g.) were left together at 15° for 10 minutes. After evaporation of volatile constituents under diminished pressure with several portions of carbon tetrachloride, the residue was distilled, to give the *diacyl* compound (1·74 g., 67%) as a syrup, b. p. 121—125° (bath-temp.)/12 mm. (Found: C, 52·2; H, 3·3; F, 25·0; CF_3·CO, 41·9. $C_{10}H_8O_2NF_3$ requires C, 51·95; H, 3·5; F, 24·7; CF_3·CO, 42·0%).

(b) *Hydrolysis.* The titration liquors from the trifluoroacetyl determination (see Bourne, Tatlow, and Tatlow, *loc. cit.*) yielded acetanilide in 69% yield.

(c) *Methanolysis.* The diacyl compound (0·171 g.) was refluxed in magnesium-dried methyl alcohol (5 c.c.) for 40 minutes before the alcohol was distilled off and the solid residue recrystallised to give acetanilide (0·066 g., 66%).

(d) *Reaction with* 2 : 5-*dichloroaniline.* This amine (0·502 g.) and the above diacyl compound (0·718 g.) were heated together at 100° for 1 hour. The residue was extracted with boiling light petroleum (b. p. 40—60°), and the insoluble portion was recrystallised from light petroleum (b. p. 100—120°), to give acetanilide (0·310 g., 74%). The solution after concentration deposited 2 : 5-dichlorotrifluoroacetanilide (0·573 g., 71%), m. p. and mixed m. p. 68°.

N-*Benzoyl*-N-*trifluoroacetyl*cyclo*hexylamine.*—(a) *Preparation.* *N-cyclo*Hexylbenzamide (1·02 g.), trifluoroacetic anhydride (6·0 g.), and sodium trifluoroacetate (0·39 g.) were refluxed for 20 minutes and then distilled at 20 mm. with several portions of carbon tetrachloride. The solid residue was extracted with boiling light petroleum (b. p. 40—60°), and the extracts were concentrated and cooled; the deposit was recrystallised twice from the same solvent, to give the *diacyl* compound (0·443 g., 29%), m. p. 81—82° (Found: C, 60·2; H, 5·2; F, 18·7; CF_3·CO, 33·3. $C_{15}H_{16}O_2NF_3$ requires C, 60·2; H, 5·4; F, 19·0; CF_3·CO, 32·4%).

(b) *Hydrolysis.* The titration liquors afforded *N-cyclo*hexylbenzamide (96%), m. p. and mixed m. p. 148°.

(c) *Methanolysis.* The diamide (0·125 g.), refluxed in dry methyl alcohol (10 c.c.) for 90 minutes, gave *N-cyclo*hexylbenzamide (0·083 g., 98%).

Infra-red Measurements on the Diacyl Derivatives.—By means of a Grubb Parsons infra-red spectrometer with a rock-salt prism, and chloroform or carbon tetrachloride as solvents, the following carbonyl stretching frequencies (cm.$^{-1}$) were recorded: acetanilide 1690, trifluoroacetanilide 1734, *N*-acetyl-*N*-trifluoroacetylaniline 1734 (one band only), *N-cyclo*hexylbenzamide 1652, *N-cyclo*hexyltrifluoroacetamide 1718, and *N*-benzoyl-*N*-trifluoroacetyl*cyclo*hexylamine 1726 and 1703. It appears that in the last derivative, the presence of the CF_3·CO residue increases the carbonyl frequency due to the C_6H_5·CO group by 51 cm.$^{-1}$. A similar increase with *N*-acetyl-*N*-trifluoroacetylaniline would result in the carbonyl frequencies due to the CH_3·CO and CF_3·CO groups lying very close together so that they would not be resolved. No evidence for the presence of C=N bonds was found from either diacyl derivative.

Preparation of 2 : 2 : 2-*Trifluoroethylamine* (with M. W. Buxton).—Trifluoroacetamide (11·5 g.) in dry ether (40 c.c.) was added dropwise during 2 hours to a cooled and stirred suspension of lithium aluminium hydride (7·6 g.) in dry ether (120 c.c.). After 16 hours at 20° the mixture was cooled in ice and cautiously treated with an excess of water. The precipitate was removed (centrifuge), and the ethereal layer was separated. The solid and the aqueous solution were extracted with more ether, and the combined ethereal layers were dried ($CaCl_2$), filtered, and treated with hydrogen chloride. The resulting precipitate, recrystallised from absolute alcohol, gave the amine hydrochloride (11·1 g., 80%), subliming rapidly at 195° (Found: C, 17·7; H, 3·7; F, 41·4. Calc. for $C_2H_5NClF_3$: C, 17·7; H, 3·7; F, 42·1%).

The hydrochloride, treated in the usual way with benzoyl chloride and sodium hydroxide solution, the precipitate being recrystallised from aqueous methyl alcohol, gave *N*-(2 : 2 : 2-*trifluoroethyl*)*benzamide* (67%), m. p. 115—116° (Found: C, 53·2; H, 3·7. $C_9H_8ONF_3$ requires C, 53·2; H, 4·0%).

Analysis.—Carbon and hydrogen analyses were carried out by the method of Belcher and Goulden (*Mikrochem. Mikrochim. Acta*, 1951, **36/37**, 679), and fluorine analyses by the method of Belcher and Tatlow (*Analyst*, 1951, **76**, 593).

The authors thank Professor M. Stacey, F.R.S., for his interest in this work, the Department of Scientific and Industrial Research for a grant in support of it, and Dr. D. H. Whiffen for carrying out the infra-red measurements.

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768. *Nitration of 2-Acetamido-5-methoxytoluene.*

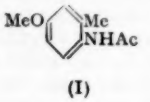
By J. MacMillan.

The preparation is described of the 3- and 4-nitro-derivatives of 2-acetamido-5-methoxytoluene. The corresponding amines, *N*-acetylanthranilic acids, and anthranilic acids have also been prepared.

Although direct comparison has confirmed the 3-nitro-structure of the nitroamine described by Dewar (*J.*, 1944, 619), the acetamido-compound, acetylanthranilic acid, and anthranilic acid to which he assigned the 3-nitro-structures have been shown to be the 4-nitro-isomers. The structures of an identical series of compounds described by Elderfield *et al.* (*J. Org. Chem.*, 1947, **12**, 405) must be similarly modified.

Mononitration of 2-acetamido-5-methoxytoluene (I) was first described by Dewar (*J.*, 1944, 619). Using nitric acid (*d* 1·5) in acetic acid below 0°, he obtained, in 70% yield, a mononitro-derivative, $C_{10}H_{12}O_4N_2$, m. p. 173—176°, raised to 187° by repeated crystallisation. The 3-nitro-structure (II; R = Ac) was assigned to this compound since hydrolysis with hydrochloric acid afforded an amine, $C_8H_{10}O_3N_2$, m. p. 134°, characterised as the *o*-nitro-amine (II; R = H) by reduction and phenanthrazine formation. Subsequently, Elderfield, Williamson, Gensler, and Kremer (*J. Org. Chem.*, 1947, **12**, 405) reported that they were unable to reproduce the high yield of (II; R = Ac) under Dewar's conditions. However, by lowering the temperature of nitration to −5°, they obtained a 65% yield of the pure mononitro-derivative, m. p. 187°, which they assumed was the 3-nitro-compound (II; R = Ac) apparently on the basis of Dewar's orientation. There

can be little doubt that the mononitro-2-acetamido-5-methoxytoluenes, described by Dewar and by Elderfield *et al.*, are identical since the series of compounds independently prepared from them possessed melting points in very close agreement.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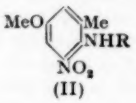
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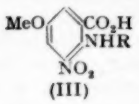
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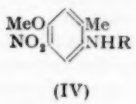
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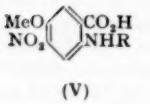
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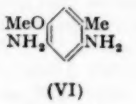
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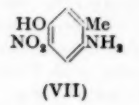
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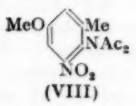
(VIII)

On repetition of the nitration of 2-acetamido-5-methoxytoluene using the method of Elderfield *et al.*, the expected mononitro-derivative (A), $C_{10}H_{12}O_4N_2$, m. p. 187°, was obtained in consistently high yield. However, hydrolysis with hydrochloric acid gave an amine (B), $C_8H_{10}O_3N_2$, m. p. 77—78°, and not the amine, m. p. 134°, described by Dewar. The amine (B) was readily re-acetylated to (A) and, on reduction, furnished a diamine (C), $C_8H_{12}ON_2$, m. p. 100°, which was not an *o*-diamine since it failed to give quinoxaline derivatives or yield a triazole on diazotisation. The close agreement in melting point between (C) and a diamine, m. p. 101°, described as 2 : 4-diamino-5-methoxytoluene (VI) by Bogacheva (*J. Appl. Chem. U.S.S.R.*, 1940, **13**, 1606) suggested that the compounds (A) and (B) were the 4-nitro-isomers (IV; R = Ac and R = H respectively). This was supported by the ease with which the methoxyl group in (A) was hydrolysed by 70% sulphuric acid, to yield an aminophenol (D), $C_7H_8O_3N_2$ (cf. Haworth and Lapworth, *J.*, 1923, **123**, 2982). Finally, the orientation of this series was firmly established by deamination of amine (B), *via* the diazonium salt, to 3-methoxy-4-nitrotoluene, identical with an authentic specimen. Compounds (A), (B), (C), and (D) therefore possess the structures (IV; R = Ac), (IV; R = H), (VI), and (VII) respectively. Accordingly, it is concluded that nitration of 2-acetamido-5-methoxytoluene, under the conditions specified by Elderfield *et al.*, affords the 4-nitro-derivative (IV; R = Ac) and not the 3-nitro-isomer (II; R = Ac) as stated by these authors.

Under Dewar's conditions of nitration, 2-acetamido-5-methoxytoluene gave a complex mixture. The main product was the 4-nitro-derivative, but all three possible dinitro-compounds were also isolated. Despite careful fractionation by crystallisation and chromatography, no trace of the 3-nitro-derivative (II; R = Ac) could be detected. The dinitro-compound, m. p. 249—251°, was shown to be the 3 : 4-dinitro-derivative by reduction and quinoxaline formation; the other two isomers which are formed in low yield were not oriented. Similar results were obtained when nitration was carried out at 20°; in this case the 3 : 4-dinitro-compound was the main product.

A surprising feature of the above results was the complete absence of the 3-nitro-isomer (II; R = Ac) although position 3 in (I) is activated by the *o*-acetamido-group. The weak but definite basic properties shown by (I) suggested that this might be due to salt formation in the acidic nitrating medium (cf. Dadswell and Kenner, *J.*, 1927, 1102). To reduce this possibility, nitration of (I) was conducted in chloroform solution. Then, at −5° to −10°, the 3-nitro-derivative (II; R = Ac), m. p. 173—174°, was obtained in 50% yield together with the 4-nitro-isomer (IV; R = Ac) (40%). The former was oriented by hydrolysis to the corresponding amine (II; R = H), m. p. 134°, which afforded a phenanthrazine after reduction. Separation of the two isomers (II and IV; R = Ac) by fractional crystallisation was difficult and was more conveniently effected by hydrolysis of the mixture to the corresponding amines which were readily separated by their widely differing solubility in mineral acid.

The 3- and the 4-nitro-amine (II and IV; R = H) differed in their ease of acetylation. With acetic anhydride in pyridine at room temperature, the 4-nitro-compound readily afforded (IV; R = Ac) while the 3-nitro-amine was unaffected. Acetylation of the latter was accomplished by acetic anhydride and acetic acid under reflux. Short heating gave

a mixture of (II; R = Ac) and the diacetyl compound (VIII), but the latter was the sole product on further heating. The constitution of (VIII) was established by hydrolysis to, and formation from, the monoacetyl compound (II; R = Ac). These observations are in accord with the behaviour of other *o*-nitro-amines towards acylating agents (Bell, *J.*, 1929, 2787).

Through the kindness of Professor M. J. S. Dewar, who is warmly thanked for placing his specimens at the author's disposal, it was possible to compare directly his amine and acetamide with their counterparts of established structure in the 3- and 4-nitro-series. His acetamido-compound was the 4-nitro-isomer (IV; R = Ac) whilst the 3-nitro-structure (II; R = H) of his nitro-amine was confirmed. This suggested that Dewar's crude product, m. p. 173—176°, was a mixture of the 3- and 4-nitro-isomers from which the latter was obtained pure only after repeated crystallisation.

Next, the 3- and 4-nitro-isomers (II and IV; R = Ac) were separately oxidised to the *N*-acetylanthranilic acids (III and V; R = Ac) respectively, and the latter compounds hydrolysed to the corresponding anthranilic acids (III and V; R = H). As might be expected, oxidation of (IV; R = Ac) took place more readily than that of (II; R = Ac). The 4-nitroanthranilic acid (V; R = H) was obtained in interconvertible very dark red and brick-red forms, both of which were unexpectedly deeper in colour than the 3-nitro-isomer (III; R = H). The structure (V; R = H) for the dimorphous anthranilic acid was, however, confirmed by deamination to 3-methoxy-4-nitrobenzoic acid.

The anthranilic acid and *N*-acetyl derivative, described by Dewar as the 3-nitro-compounds (III; R = H and Ac), were shown by direct comparison to be identical with the acids (V; R = H and Ac). Therefore the nitro-4-chloro-6-methoxyquinazoline and intermediate compounds prepared by Dewar (*loc. cit.*) are derived from 2-acetamido-5-methoxy-4-nitrotoluene (IV; R = Ac) and not from the 3-nitro-isomer (II; R = Ac).

The same considerations almost certainly apply to an identical series of compounds independently described by Elderfield *et al.* (*loc. cit.*). There seems little doubt that the amino-6-methoxyquinazoline and derivatives described by these authors possess the 7-amino-structure and therefore are not quinazoline analogues of plasmoquine.

Experimental

M. p.s are uncorrected. Microanalyses were carried out by Drs. Weiler and Strauss, Oxford, and by Mr. W. Brown.

2-Acetamido-5-methoxytoluene, m. p. 134°, prepared from 3-methoxy-6-nitrotoluene (Cook, Dickson, Ellis and Loudon, *J.*, 1949, 1074) by reduction and acetylation, readily dissolved in 4N-hydrochloric acid. From this solution it was precipitated by addition of water, redissolving on addition of concentrated hydrochloric acid. Treatment of its benzene solution with hydrogen chloride gave an air-sensitive hydrochloride.

Nitration of 2-*Acetamido-5-methoxytoluene* (I).—(*a*) The procedure of Elderfield *et al.* (*loc. cit.*) gave 2-*acetamido-5-methoxy-4-nitrotoluene* (IV; R = Ac), long pale yellow needles (65—70%), m. p. 187°, from ethyl acetate (Found: C, 53·6; H, 5·5; N, 12·5. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%). It was identical (mixed m. p., infra-red spectrum, and dielectric constant) with the nitro-2-acetamido-5-methoxytoluene described by Dewar (*loc. cit.*).

(*b*) The crude dried product (8 g.), m. p. 125—190°, obtained by nitration of 2-acetamido-5-methoxytoluene (6·7 g.) under Dewar's conditions (*loc. cit.*), was finely powdered and extracted with cold chloroform (150 ml.). The chloroform-insoluble fraction crystallised from acetic acid in small yellow needles (1·1 g.), m. p. 249—251° (decomp.), of 2-*acetamido-5-methoxy*-3 : 4-*dinitrotoluene* (Found: C, 44·8; H, 4·2; N, 16·0. $C_{10}H_{11}O_6N_3$ requires C, 44·6; H, 4·1; N, 15·6%). The *quinoxaline*, prepared by reaction of the crude, Raney nickel reduction product of the 3 : 4-dinitro-compound with benzil, crystallised in yellow needles, m. p. 229—230°, from methanol (Found: C, 75·1; H, 5·8; N, 11·1. $C_{24}H_{21}O_2N_3$ requires C, 75·2; H, 5·5; N, 11·0%).

Hydrolysis of the 3 : 4-dinitro-compound (1·0 g.) with concentrated hydrochloric acid (3 ml.) in methanol (12 ml.) by boiling under reflux (12 hours) gave 2-*amino-5-methoxy*-3 : 4-*dinitrotoluene*, long red needles, m. p. 174—175°, from benzene (Found: C, 42·1; H, 4·1; N, 18·2. $C_9H_9O_5N_3$ requires C, 42·3; H, 4·0; N, 18·5%).

The chloroform-soluble fraction of the crude nitration product partly crystallised from ethyl acetate in long pale yellow needles (2·3 g.), m. p. and mixed m. p. with 2-acetamido-5-methoxy-

4-nitrotoluene, obtained as in (*a*), 187°. Concentration of the ethyl acetate mother-liquors gave 1·2 g. of material, m. p. 140—160°, which was separated into a benzene-insoluble and a benzene-soluble fraction. Chromatography of the latter in benzene (100 ml.) on alumina (pH 4; 1·0 × 12·5 cm.), activated at 250°/15 mm. for 3 hours, and elution with benzene gave (i) the 3 : 4-dinitro-compound (5 mg.), m. p. 249—251° (decomp.), (ii) *2-acetamido-5-methoxy-4(or 3) : 6-dinitrotoluene*, pale yellow needles (65 mg.), m. p. 166—168°, from methanol (Found: C, 45·0; H, 4·2; N, 15·6. $C_{10}H_{11}O_6N_3$ requires C, 44·7; H, 4·1; N, 15·6%), and (iii) *2-acetamido-5-methoxy-3(or 4) : 6-dinitrotoluene*, yellow needles (50 mg.), m. p. 232—234°, from acetic acid, depressed below 218° on admixture with fraction (i) (Found: C, 44·6; H, 4·1; N, 16·3%). From the benzene-insoluble fraction there were isolated, by successive crystallisation from acetic acid, ethyl acetate, and methanol, the 3 : 4-dinitro- (1 mg.), m. p. 249—251° (decomp.), the 4(or 3) : 6-dinitro- (15 mg.), m. p. 166—168°, and the 4-nitro-derivative (2 mg.), m. p. 187°.

(*c*) Nitration was effected as in (*a*), but with the temperature kept at 20° during the addition of 2-acetamido-5-methoxytoluene (6·7 g.) and for a further ½ hour. The crystalline material which separated at room temperature overnight was collected and recrystallised from acetic acid in small yellow needles (2·4 g.) of the 3 : 4-dinitro-compound, m. p. 249—251° (decomp.). Dilution of the reaction mother-liquors and fractional crystallisation of the resultant precipitate from methanol yielded (i) the 3 : 4-dinitro- (500 mg.), m. p. 249—251° (decomp.), (ii) the 4-nitro- (1·3 g.), m. p. 187°, (iii) the 4(or 3) : 6-dinitro- (500 mg.), m. p. 166—168°, and (iv) the 3(or 4) : 6-dinitro-compound (10 mg.), m. p. 232—234°.

(*d*) A solution of 2-acetamido-5-methoxytoluene (5 g.) in chloroform (30 ml.) was kept between −5° and −10° while nitric acid (8·5 ml.; *d* 1·42) was added during 1½ hours. After a further 1½ hours' stirring at −5° to −10°, water (50 ml.) was added and the solid (A) which separated on stirring was collected. The chloroform layer, after separation from the aqueous layer, was again washed with water (50 ml.). Overnight, more solid (B) separated. Finally, concentration of the chloroform layer after further washing yielded a third fraction (C).

Fraction (A) consisted of the 4-nitro-compound (IV; R = Ac)(1·1 g.), m. p. 187°. Crystallisation of fraction (B) from ethyl acetate afforded *2-acetamido-5-methoxy-3-nitrotoluene* (II; R = Ac), in long pale yellow needles (1·35 g.), m. p. 173—174° (Found: C, 53·75; H, 5·3; N, 12·4%).

The materials recovered from the mother-liquors of fractions (A) and (B) were combined with fraction (C) and hydrolysed by concentrated hydrochloric acid (6 ml.) and methanol (25 ml.) under reflux for 8 hours. On cooling, ruby-red prisms (1·4 g.), m. p. 134°, were obtained of 2-amino-5-methoxy-3-nitrotoluene (see below). Basification of the mother-liquors with sodium carbonate, after removal of the methanol, gave 2-amino-5-methoxy-4-nitrotoluene (0·6 g.), m. p. 77—78°, described below.

2-Amino-5-methoxy-4-nitrotoluene (IV; R = H).—2-Acetamido-5-methoxy-4-nitrotoluene (2·25 g.), in methanol (22·5 ml.), was heated under reflux for 6 hours with 2N-hydrochloric acid (22·5 ml.). The *hydrochloride* which separated on cooling crystallised from 2N-hydrochloric acid in straw-coloured needles (2·0 g.), decomp. >200° (Found: C, 43·85; H, 4·9; N, 13·0; Cl, 16·35. $C_8H_{11}O_3N_2Cl$ requires C, 43·9; H, 5·0; N, 12·8; Cl, 16·3%). The free *amine*, obtained by decomposition of the hydrochloride with aqueous sodium carbonate, was combined with a small quantity recovered from the basified reaction mother-liquors and crystallised from benzene in deep red prisms (1·8 g.), m. p. 77—78° (Found: C, 52·5; H, 5·6; N, 15·1. $C_8H_{10}O_3N_2$ requires C, 52·7; H, 5·5; N, 15·4%). Treatment of the amine in pyridine with acetic anhydride at room temperature overnight gave 2-acetamido-5-methoxy-4-nitrotoluene, m. p. 187°, identified by mixed m. p. and infra-red spectrum.

Deamination was effected by addition of cold hypophosphorous acid (10 ml.) to a filtered and ice-cold diazo-solution of the amine (400 mg.). After 2 days at 0°, the precipitate was collected and crystallised from light petroleum (b. p. 40—60°) in fawn-coloured needles, m. p. 58—59°, undepressed on admixture with 3-methoxy-4-nitrotoluene, obtained by methylation of 3-hydroxy-4-nitrotoluene in methanol with diazomethane.

2-Amino-5-hydroxy-4-nitrotoluene (VII).—2-Acetamido-5-methoxy-4-nitrotoluene (500 mg.) was heated under reflux for 1 minute with 70% sulphuric acid (2 ml.). The diluted red-brown solution was adjusted to pH 7·5 and the resultant *aminophenol* crystallised from benzene in dark red prisms, m. p. 126—127° (Found: C, 50·1; H, 4·75; N, 16·4. $C_7H_8O_3N_2$ requires C, 50·0; H, 4·7; N, 16·7%); the *diacetyl* derivative formed yellow needles (from ethyl acetate), m. p. 187°, depressed below 160° on admixture with 2-acetamido-5-methoxy-4-nitrotoluene (Found: C, 52·4; H, 4·8; N, 11·1. $C_{11}H_{12}O_5N_2$ requires C, 52·4; H, 4·8; N, 11·1%).

2 : 4-Diamino-5-methoxytoluene (VI).—2-Amino-5-methoxy-4-nitrotoluene (600 mg.) in

methanol (50 ml.) was hydrogenated with Raney nickel (1·0 g.) at room temperature and pressure. Removal of the catalyst and concentration gave a violet-tinged gum from which the *diamine* was obtained as colourless needles, m. p. 100°, from benzene (charcoal) (Found : C, 63·1; H, 8·1; N, 18·5. $C_8H_{12}ON_2$ requires C, 63·1; H, 7·9; N, 18·4%); the *diacetyl* derivative crystallised in colourless needles, m. p. 215—217°, from aqueous methanol (Found : C, 56·3, 56·8; H, 6·9, 6·9; N, 11·4, 11·0. $C_{12}H_{16}O_3N_2,H_2O$ requires C, 56·7; H, 7·1; N, 11·0%). The diacetyl compound, m. p. 215—217°, was also prepared by acetylation of 2-*acetamido*-4-*amino*-5-*methoxytoluene*, colourless needles, m. p. 177—178°, from ethanol (Found : C, 62·0; H, 7·2; N, 14·6. $C_{10}H_{14}O_2N_2$ requires C, 61·85; H, 7·2; N, 14·4%), which in turn was prepared by reduction of 2-acetamido-5-methoxy-4-nitrotoluene in ethanol with Raney nickel.

2-*Amino*-5-*methoxy*-3-*nitrotoluene* (II; R = H).—2-Acetamido-5-methoxy-3-nitrotoluene (500 mg.) in methanol (6 ml.) was heated under reflux for 8 hours with concentrated hydrochloric acid (2 ml.). The 3-*nitro-amine*, which separated on cooling, crystallised from ethyl acetate in ruby-red prisms (370 mg.), m. p. 134°, undepressed on admixture with a sample of the amine, m. p. 134°, described by Dewar (*loc. cit.*) (Found : C, 52·9; H, 5·4; N, 15·2. Calc. for $C_8H_{10}O_3N_2$: C, 52·7; H, 5·5; N, 15·4%). The *phenanthrazine*, obtained by reduction of the nitro-amine with Raney nickel followed by reaction with phenanthraquinone, crystallised from 2-methoxyethanol in fawn-coloured needles, m. p. and mixed m. p. with a sample of Dewar's phenanthrazine, 218—219° (Found : C, 81·8; H, 5·3; N, 8·7. Calc. for $C_{22}H_{16}ON_2$: C, 81·5; H, 5·0; N, 8·6%).

Acetylation of 2-*Amino*-5-*methoxy*-3-*nitrotoluene*.—(*a*) The amine (100 mg.) in acetic acid (0·3 ml.) was heated under reflux for ½ hour with acetic anhydride (0·2 ml.). Dilution of the mixture and crystallisation of the product from ethyl acetate afforded 2-acetamido-5-methoxy-3-nitrotoluene, m. p. 173—174°. The solid recovered from the ethyl acetate mother-liquors crystallised from benzene–light petroleum (1 : 1) in pale yellow needles of 2-NN-*diacetylamino*-5-*methoxy*-3-*nitrotoluene*, m. p. 88—89° (Found : C, 54·1; H, 5·4; N, 10·5. $C_{12}H_{14}O_5N_2$ requires C, 54·1; H, 5·3; N, 10·5%). Chromatography of the diacetyl derivative in benzene on alumina (pH 4) and elution of the yellow band of general absorption with benzene gave 2-acetamido-5-methoxy-3-nitrotoluene, m. p. and mixed m. p. 173—174°.

(*b*) When heating was continued for 4 hours, the diacetyl compound, m. p. 88—89°, was the sole product. It was also obtained from 2-acetamido-5-methoxy-3-nitrotoluene under these conditions.

N-*Acetyl*-5-*methoxy*-4-*nitroanthranilic Acid* (V; R = Ac).—Finely powdered 2-acetamido-5-methoxy-4-nitrotoluene (400 mg.), suspended in water (30 ml.) containing magnesium sulphate (600 mg. of heptahydrate), was oxidised with potassium permanganate (850 mg.) at 70—80° as described by Dewar (*loc. cit.*). The N-*acetyl-acid* crystallised from acetic acid in small chrome-yellow needles (330 mg.), m. p. 248—250° (decomp.) (Found : C, 47·2; H, 4·1; N, 11·0%; equiv., 266. $C_9H_8O_4N_2{\cdot}CO_2H$ requires C, 47·2; H, 4·0; N, 11·0%; equiv., 254).

N-*Acetyl*-5-*methoxy*-3-*nitroanthranilic Acid* (III; R = Ac).—2-Acetamido-5-methoxy-3-nitrotoluene (360 mg.) was oxidised as above except that the suspension was heated under reflux for 5 hours. The N-*acetyl-acid*, recovered from a sodium hydrogen carbonate extract of the crude product, crystallised from water containing acetic acid in orange needles (50 mg.), m. p. 206—208° (decomp.) (Found : C, 47·8; H, 4·0; N, 11·3%). Starting material (200 mg.) was recovered unchanged.

5-*Methoxy*-4-*nitroanthranilic Acid* (V; R = H).—*N*-Acetyl-4-nitroanthranilic acid (80 mg.) was hydrolysed as described by Dewar (*loc. cit.*). The *anthranilic acid* crystallised from methanol containing a little water in long, dark red needles and from water containing a little methanol in brick-red needles. Each form was readily converted into the other by crystallisation from the appropriate solvent with seeding. The darker form was converted into the lighter at 170—180°; both melted at 220—222° (decomp.) (Found : C, 45·7; H, 3·8; N, 13·5. $C_8H_8O_5N_2$ requires C, 45·3; H, 3·8; N, 13·2%). The red-black modification was identical (mixed m. p. and infra-red spectrum) with the anthranilic acid described by Dewar.

Deamination by treatment of a diazo-solution of the anthranilic acid with hypophosphorous acid afforded 3-methoxy-4-nitrobenzoic acid, m. p. 227—229°, identical (mixed m. p. and infra-red spectrum) with an authentic specimen prepared by oxidation of 3-methoxy-4-nitrotoluene.

5-*Methoxy*-3-*nitroanthranilic Acid* (III; R = H).—*N*-Acetyl-3-nitroanthranilic acid (70 mg.), in methanol (2 ml.), was heated under reflux for ¼ hour with concentrated hydrochloric acid (2 ml.). The *amino-acid*, recovered from a bicarbonate extract of the resultant solid, crystallised from methanol in scarlet needles, m. p. 240—242° (Found : C, 45·5; H, 3·6; N, 13·25%). The neutral material crystallised from methanol in fine red needles, m. p. 141—

142°. It contained nitrogen and a carbonyl group (infra-red) but there was insufficient for characterisation.

The author is indebted to Professor Sir Robert Robinson, F.R.S., for making available Professor M. J. S. Dewar's specimens, to Dr. J. D. Loudon for the gift of 3-hydroxy-4-nitrotoluene, to Dr. L. A. Duncanson for infra-red absorption comparisons, to Dr. R. G. Wilkins for dielectric constant measurements, and to Mr. P. J. Suter for technical assistance.

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769. *Synthesis of* NN-*Dialkyl*-N′-*benzyl*(*or -ethyl*)-N′-1(*or* 2)-*naphthylethylenediamines as Potential Histamine Antagonists.*

By N. B. Chapman, J. W. James, and J. F. A. Williams.

The preparation and pharmacological properties are described of eight fully substituted ethylenediamines containing the group $\cdot[CH_2]_2\cdot NR_2$ (R = Me, Et), and bearing 1- or 2-naphthyl radicals, and ethyl or benzyl radicals on the second nitrogen atom. None of them is very active as a histamine antagonist.

During the last two decades the synthesis of compounds specifically antagonising the effects of histamine on the animal organism has been intensively studied (for recent reviews see Idson, *Chem. Reviews*, 1950, **47**, 307; Adamson, *Chem. and Ind.*, 1951, 2). The object of the investigation to be described is to explore a small previously unexamined portion of the field.

Ethylenediamines fully substituted on the nitrogen atoms were early shown to be active against histamine (Staub, *Ann. Inst. Pasteur*, 1939, **63**, 400, 420, 485), and in particular " Antergan " (I) proved to have properties which, despite unwanted side effects, marked the first significant step in the therapy of allergic diseases.

$Ph\cdot N(CH_2Ph)\cdot[CH_2]_2\cdot NMe_2$ (I) $\quad 1\text{-}C_{10}H_7\cdot NR'\cdot[CH_2]_2\cdot NR_2$ (II) $\quad 2\text{-}C_{10}H_7\cdot NR'\cdot[CH_2]_2\cdot NR_2$ (III)

It seemed worthwhile, therefore, to see whether loading one aryl residue more heavily than previously, as in (II) and (III) (R′ = CH_2Ph; R = Me, Et), would lead to a substance with an action more persistent than that of " Antergan." In a related field an analogous structural alteration had been shown to give an increase in activity, *viz.*, " Dibenamine," $(CH_2Ph)_2N\cdot CH_2\cdot CH_2\cdot Cl$, is less active than $1\text{-}C_{10}H_7\cdot CH_2\cdot NEt\cdot CH_2\cdot CH_2Cl$ (Nickerson and Gump, *J. Pharmacol.*, 1949, **67**, 25). After most of the work had been completed, there appeared an account of a more comprehensive investigation on similar lines (Grail, Tenenbaum, Tolstoouhov, Duca, Reinhard, Anderson, and Scudi, *J. Amer. Chem. Soc.*, 1952, **74**, 1313), to which the present paper is supplementary.

Synthesis of compounds of the types (II) and (III) gave no trouble when R′ = CH_2Ph, R = Me or Et, and of (II) when R′ = Et, R = Me or Et. Heating secondary alkylarylamines with sodamide in toluene or xylene yields sodium salts, which may be expeditiously condensed with 2-dialkylaminoethyl chlorides to yield the required compounds (cf. Leonard and Solmssen, *ibid.*, 1948, **70**, 2066). However, *N*-ethyl-2-naphthylamine presented unexpected difficulties, for the intermediate sodium salt proved unstable towards even traces of oxygen. The preparation and handling this salt are described in the Experimental section.

In a provisional pharmacological report, J. D. P. Graham, G. P. Lewis, and R. S. Tonks, of the Department of Pharmacology, Welsh National School of Medicine, Cardiff, report that the structural variation studied has virtually abolished anti-histamine activity, and that in accordance with common experience the side chain $\cdot[CH_2]_2\cdot NMe_2$ affords greatest activity. For the compounds (II) and (III) where R′ = benzyl, replacing 1-naphthyl by 2-naphthyl or R = Me by R = Et roughly halves the toxicity in each case, whereas the opposite is true for compounds in which R′ = Et. A fuller account of the

pharmacological investigation will be published elsewhere, but preliminary quantitative data are given in the Experimental section.

Because of the insolubility and lack of the desired activity of this class of compound, the investigation is being developed in other directions.

Experimental

Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected. L.D.$_{50}$'s after 1 hour (mg. per kg., mice), by intra-peritoneal administration in phosphate-citrate buffer at pH 5·4, are given below.

2-Dimethyl- and 2-Diethyl-aminoethyl Chloride Hydrochloride.—A procedure similar to that described in *Org. Synth.*, **31**, 37, but worked out before that account appeared, was adopted after considerable investigation, details in the literature being unsatisfactory. We found it advisable, however, to distil the thionyl chloride before use to remove hydrogen chloride, to dry commercial 2-dialkylaminoethanols over barium oxide, then fractionate them (25-cm. Fenske column), and to carry out the reaction in dry benzene. The free bases were best liberated from their salts by Knorr's method (*Ber.*, 1904, **37**, 3511).

N-Benzyl-N′N′-dimethyl-N-1-naphthylethylenediamine (II; R′ = CH_2Ph, R = Me).—1- and 2-Benzylaminonaphthalene were prepared by Zechmeister and Truka's method (*Ber.*, 1930, **63**, 2883), *viz.*, reduction of the corresponding benzylidene compounds with magnesium and methanol, in 89 and 93% yields respectively. Sodamide (4·1 g., 0·11 mol.) was stirred with a boiling solution of 1-benzylaminonaphthalene in dry toluene (5 hours), whereupon the yellow sodium salt separated. A solution of 2-dimethylaminoethyl chloride (10·8 g., 0·11 mol.) in dry toluene (10 c.c.) was added dropwise (4 hours) and the mixture boiled for a further 6 hours. After filtration and removal of toluene at 15 mm., an excess of hydrochloric acid (50% w/v) was added and unchanged 1-benzylaminonaphthalene filtered off. Addition of aqueous sodium hydroxide, extraction with ether, drying (Na_2SO_4), and removal of ether yielded (61%) as a viscous yellow oil, *N-benzyl-N′N′-dimethyl-N-1-naphthylethylenediamine*, b. p. 146°/0·007 mm., n_D^{20} 1·6090, L.D.$_{50}$ 135 (Found: C, 82·7; H, 8·3; N, 8·4. $C_{21}H_{24}N_2$ requires C, 82·8; H, 7·9; N, 9·2%); the *picrate* (from ethanol) had m. p. 173·5° (Found: C, 60·9; H, 5·0; N, 13·6. $C_{27}H_{27}O_7N_5$ requires C, 60·7; H, 5·1; N, 13·1%); the *monohydrobromide* (from alcohol) had m. p. 170° (Found: Br, 21·1. $C_{21}H_{24}N_2$,HBr requires Br, 20·7%).

N-Benzyl-N′N′-dimethyl-N-2-naphthylethylenediamine (III; R′ = CH_2Ph, R = Me) was prepared (65%) as was the 1-naphthyl compound, save that the sodium salt of 2-benzylaminonaphthalene was formed at the b. p. of dry xylene and the mixture cooled to 110° before addition of 2-dimethylaminoethyl chloride, which is unstable at the b. p. of xylene. *N-Benzyl-N′N′-dimethyl-N-2-naphthylethylenediamine* was a viscous yellow oil, b. p. 146°/0·007 mm., n_D^{20} 1·6302, L.D.$_{50}$ 265 (Found: C, 82·1; H, 8·0; N, 9·45%). The *picrate* (from acetone–ethanol) had m. p. 110° (decomp.) (Found: N, 12·9%), and the *monohydrobromide* (from ethanol) had m. p. 186° (Found: Br, 20·9%).

N-Benzyl-N′N′-diethyl-N-1-naphthylethylenediamine (II; R′ = CH_2Ph, R = Et), prepared (55%) as for the dimethyl analogue, had b. p. 140°/0·003 mm., n_D^{20} 1·5974, L.D.$_{50}$ 62·5 (Found: C, 83·6; H, 8·3; N, 8·6. $C_{23}H_{28}N_2$ requires C, 83·1; H, 8·5; N, 8·4%). Its *monohydrobromide monohydrate* (from aqueous ethanol) had m. p. 191° (Found: Br, 18·7. $C_{23}H_{28}N_2$,HBr,H_2O requires Br, 18·5%).

The *2-naphthyl* isomer, prepared (55%) as for the dimethyl analogue, had b. p. 140°/0·0015 mm., n_D^{20} 1·6110, L.D.$_{50}$ 128 (Found: C, 82·7; H, 8·7; N, 8·4%).

Its *monohydrobromide* (from ethanol) had m. p. 165° (Found: Br, 20·2. $C_{23}H_{28}N_2$,HBr requires Br, 19·2%).

N-Ethyl-N′N′-dimethyl-N-1-naphthylethylenediamine (II; R′ = Et, R = Me).—1-Ethylaminonaphthalene (from British Drug Houses Ltd.; 27·6 g., ~0·16 mol.) was dried (KOH) and redistilled, and was dissolved in xylene (320 c.c.), and sodamide (6·5 g., ~0·16 mol.) was added. The mixture was boiled with stirring for 7 hours, then cooled to ~90°, and dimethylaminoethyl chloride (20 g., 0·14 mol.) slowly added and the mixture boiled for 1 hour. After filtration of the hot liquor and removal of the xylene at 15 mm., the residue was fractionated through a 9″ heated Vigreux column, or a 9″ column packed with Dixon gauze rings fitted with a variable-temperature vapour-jacket. Refractionation yielded (34%) *N-ethyl-N′N′-dimethyl-N-1-naphthylethylenediamine*, a brown oil with blue fluorescence, b. p. 174—175°/0·13 mm., n_D^{23} 1·5741, L.D.$_{50}$ 121 (Found: C, 79·2; H, 9·1; N, 11·7. $C_{16}H_{22}N_2$ requires C, 79·3; H, 9·1; N, 11·6%). It gave a *dipicrate monohydrate*, m. p. 162° (decomp.) (Found: C, 45·9; H, 3·55; N, 15·6. $C_{28}H_{30}O_{15}N_8$ requires C, 46·0; H, 4·11; N, 15·3%).

N-*Ethyl*-N'N'-*dimethyl*-N-2-*naphthylethylenediamine* (III; R' = Et, R = Me).—This was similarly prepared (15%) from 2-ethylaminonaphthalene (Hickinbottom "Reactions of Organic Compounds," Longmans, Green, & Co., London, 1936, p. 300). It is essential to prepare the sodium salt under oxygen-free nitrogen and advisable to keep the temperature about 50° and not to stir the mixture. The yellow sodium salt is readily formed at room temperature and is noticeably soluble in xylene. The dimethylaminoethyl chloride was added to the mixture at 50° after 4 hours, and the reaction completed at 80° during 1 hour. N-*Ethyl*-N'N'-*dimethyl*-N-2-*naphthylethylenediamine* was a brown oil, with blue fluorescence, especially noticeable in ethanolic solution, and had b. p. 159°/0·08 mm., n_D^{18} 1·6100, L.D.$_{50}$ 52 (Found: C, 79·4; H, 9·0; N, 11·3%). Its *dipicrate* (from ethanol) had m. p. 174—175° (decomp.; sinters at ~160°) (Found: C, 47·8; H, 3·95; N, 15·5. $C_{28}H_{28}O_{14}N_8$ requires C, 47·2; H, 3·55; N, 15·7%).

NN'N'-*Triethyl*-N-1-*naphthylethylenediamine*, prepared (42%) as for the dimethyl analogue, had b. p. 182°/0·13 mm., n_D^{21} 1·5598, L.D.$_{50}$ 65 (Found: C, 80·2; H, 9·3; N, 10·5. $C_{18}H_{26}N_2$ requires C, 80·0; H, 9·6; N, 10·4%). Its *dipicrate* (from ethanol) had m. p. 110—111° (Found: C, 49·3; H, 4·4; N, 14·9. $C_{30}H_{32}O_{14}N_8$ requires C, 48·7; H, 4·3; N, 15·1%).

The 2-*naphthyl* isomer, prepared (16%) under the same rigorous conditions as the dimethyl analogue, had b. p. 180°/0·2 mm., n_D^{17} 1·5950, L.D.$_{50}$ 36 (Found: C, 80·1; H, 9·7; N, 10·7%), and its *dipicrate* (from ethanol) had m. p. 160° (Found: C, 49·4; H, 4·3; N, 15·4%).

The last two bases are similar in colour and fluorescence to the dimethyl analogues.

Pharmacological Activity.—Antihistamine activity determined by the cat blood pressure or guinea-pig aerosol method is very slight for all the compounds except (II; R = Me, R' = CH_2Ph) which has an activity of about 1/20 of that of "Neoantergan."

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THE UNIVERSITY, SOUTHAMPTON. [*Received, June 25th*, 1952.]

770. *Alicyclic Glycols. Part VI.* Derivatives of* cyclo*Pentane*-1 : 2-*diol.*

By L. N. OWEN and PETER N. SMITH.

The following derivatives of the *trans*-diol are prepared by reaction of *cyclo*pentene oxide with the appropriate acid: *trans*-2-chloro-, -2-bromo-, -2-iodo-, -2-acetoxy-, -2-methanesulphonyloxy-, and -2-toluene-*p*-sulphonyloxy-*cyclo*pentanol. The monoacetate of the *cis*-diol is obtained by reaction of *trans*-2-toluene-*p*-sulphonyloxy*cyclo*pentyl acetate with alcoholic potassium acetate, according to the method used by Winstein in the *cyclo*hexane series. Reaction of the *trans*-monotoluene-*p*-sulphonate with sodium iodide, lithium bromide, or lithium chloride gives the *trans*-2-halogeno-*cyclo*pentanol; *trans*-2-chloro*cyclo*pentanol is also obtained from the *cis*-monotoluene-*p*-sulphonate and lithium chloride. The steric results of these substitutions are the same as in the *cyclo*hexane field, and indicate that Winstein's neighbouring-group effect applies also to *cyclo*pentane compounds. Alkaline hydrolysis of the *trans*-monotoluene-*p*-sulphonate gives *cyclo*pentene oxide, and proceeds several hundred times faster than with the *cis*-isomer, which gives *cyclo*pentanone; both derivatives are considerably more reactive than their *cyclo*hexane analogues.

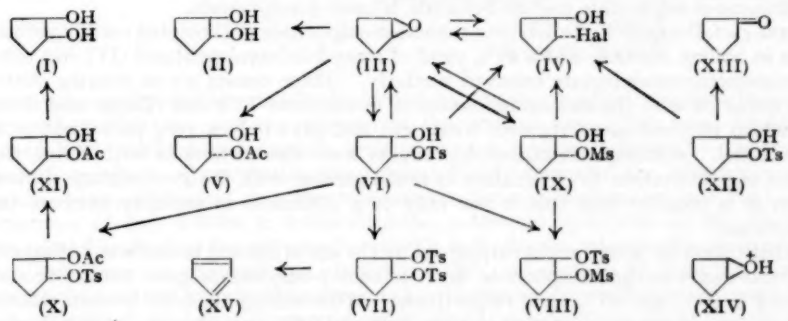
THE participation of toluene-*p*-sulphonyl and methanesulphonyl derivatives of *cyclo*hexane-1 : 2-, -1 : 3-, and -1 : 4-diols in substitution and elimination reactions has been described in earlier publications in this series (Clarke and Owen, *J.*, 1949, 315; 1950, 2103; Owen and Robins, *J.*, 1949, 320). In this and the following paper the preparation and reactions of derivatives of *cyclo*pentane-1 : 2- and -1 : 3-diols will be considered, and their behaviour compared with that of their *cyclo*hexane analogues.

* Part V, Clarke and Owen, *J.*, 1950, 2108.

The liquid *cis*- (I) and the solid *trans*-forms (II) of *cyclo*pentane-1 : 2-diol have been known for many years, and their configurations are established (see, *inter al.*, Böesken, *Rec. Trav. chim.*, 1928, **47**, 683; Helferich and Hiltmann, *Ber.*, 1937, **70**, 308). In the present investigation, the use of performic acid (cf. Swern, Billen, Findley, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786) for the hydroxylation of *cyclo*pentene gave the *trans*-diol in 64% yield; with peracetic acid only 37% was attained. The *cis*-diol was prepared by low-temperature hydroxylation of *cyclo*pentene with neutral aqueous potassium permanganate; the mild conditions resulted in a higher yield (34%) than has previously been recorded (cf. Böeseken, *loc. cit.*). Other methods of *cis*-hydroxylation also studied were the interaction of *cyclo*pentene with (i) anhydrous hydrogen peroxide in *tert.*-butanol in the presence of osmic acid (cf. Milas and Sussman, *J. Amer. Chem. Soc.*, 1936, **58**, 1302), and (ii) aqueous sodium chlorate with osmic acid as catalyst (cf. Milas and Terry, *ibid.*, 1925, **47**, 1412; Milas, *ibid.*, 1927, **49**, 2005), but the yields under the usual conditions were 2·5% and nil, respectively, in marked contrast to the results obtained with *cyclo*hexene, 58% and 44% respectively (*idem, ibid.*, 1937, **59**, 2345; Clarke and Owen, *J.*, 1949, 315).

Treatment of *cis*- and *trans*-*cyclo*pentane-1 : 2-diol with excess of toluene-*p*-sulphonyl chloride or methanesulphonyl chloride in pyridine gave the *cis*- and the *trans*-ditoluene-*p*-sulphonate and dimethanesulphonate, all four derivatives being solid. The *cis*- and the *trans*-dimethanesulphonate had identical melting points (82°), but showed marked depression on admixture.

For the preparation of mono-derivatives of a *trans*-diol, the most convenient method is often the fission of the corresponding epoxide with an appropriate reagent. The necessary *cyclo*pentene oxide (III) was prepared by dehydrohalogenation of the *trans*-chlorohydrin (IV) obtained by addition of hypochlorous acid to *cyclo*pentene; only a small amount of the *cis*-chlorohydrin is formed in the latter reaction (Godchot, Mousseron, and Granger, *Compt. rend.*, 1935, **200**, 748). Attempts to prepare the *cis*-chlorohydrin by reduction of 2-chloro-*cyclo*pentanone with *tert.*-butylmagnesium chloride, following the method used by Bartlett and Rosen (*J. Amer. Chem. Soc.*, 1935, **57**, 224) for the *cyclo*hexane analogue, were unsuccessful. Reduction of 2-chloro*cyclo*pentanone with aluminium *iso*propoxide in *iso*propyl alcohol gave a mixture of *cyclo*pentanol and *cis*-2-chloro*cyclo*pentanol. In the corresponding reduction of 2-chloro*cyclo*hexanone, Mousseron and Combes (*Bull. Soc. chim.*, 1947, 604) obtained *cyclo*hexanol together with *cis*- and *trans*-2-chloro*cyclo*hexanol.



(Ts = *p*-$C_6H_4Me{\cdot}SO_2^-$; Ms = $Me{\cdot}SO_2^-$)

Stereochemically pure *trans*-2-halogeno*cyclo*pentanols were prepared by reaction of *cyclo*pentene oxide with anhydrous hydrogen chloride, bromide, and iodide, in ether. Each halogenohydrin gave a crystalline *p*-nitrobenzoate, and also reacted readily with aqueous alkali (or aqueous silver nitrate in the case of the iodohydrin) to give *cyclo*pentene oxide. Whilst the *trans*-chlorohydrin had previously been characterised, the bromo- and iodo-compounds were hitherto ill-defined and no solid derivatives had been reported.

Reaction of *cyclo*pentene oxide with acetic acid at 100° gave a 40% yield of the *trans*-

monoacetate (V), which was also obtained (yield 17%) by reaction of peracetic acid with *cyclo*pentene.

Criegee and Stanger (*Ber.*, 1936, **69**, 2753) obtained a 10% yield of a liquid toluene-*p*-sulphonate, which was not identified, by treatment of *cyclo*pentene oxide with toluene-*p*-sulphonic acid in ether. Under apparently similar conditions we have obtained a 69% yield of *trans-cyclo*pentane-1 : 2-diol monotoluene-*p*-sulphonate (VI), characterised by conversion into the crystalline *trans*-ditoluene-*p*-sulphonate (VII), *trans*-methanesulphonate toluene-*p*-sulphonate (VIII), and *trans*-benzoate toluene-*p*-sulphonate. The *trans*-monomethanesulphonate (IX) was prepared in 59% yield by reaction of the oxide with ethereal methanesulphonic acid; it was characterised by conversion into the *trans*-dimethanesulphonate and into (VIII).

Mono-derivatives of the *cis*-diol were more difficult to obtain. Attempted monoacetylation, by the gradual addition of 1 mol. of acetic anhydride to a dilute solution of the diol in pyridine at 0°, gave a mixture, containing some diacetate, which could not easily be separated. Winstein, Hess, and Buckles, however, have shown (*J. Amer. Chem. Soc.*, 1942, **64**, 2796) that the acetate toluene-*p*-sulphonate of *trans-cyclo*hexane-1 : 2-diol, on treatment with potassium acetate in ethanol, gives the *cis*-monoacetate, this steric result being due to the intermediate formation of a cyclic ethyl orthoacetate. The *trans*-monotoluene-*p*-sulphonate (VI) was therefore acetylated to give (X), which when treated with boiling alcoholic potassium acetate gave the pure *cis*-monoacetate (XI) in 44% yield; the configuration was proved by deacetylation to the *cis*-diol (I) and characterisation of the latter.

The monosulphonates of *cis-cyclo*hexane-1 : 2-diol had been obtained (Clarke and Owen, *J.*, 1949, 315) by toluene-*p*-sulphonation or methanesulphonation of the *cis*-monoacetate, followed by deacetylation with methanolic hydrogen chloride. This procedure was therefore applied to the *cis*-monoacetate (XI), but as neither the *cis*-acetate toluene-*p*-sulphonate nor the deacetylated material could be crystallised or distilled the *cis*-monotoluene-*p*-sulphonate was not obtained pure. A more satisfactory method was the treatment of a pyridine solution of the *cis*-diol with 1 mol. of toluene-*p*-sulphonyl chloride in chloroform, added over a period of 3 days; this gave the pure mono-derivative (XII) in 40% yield. Under these conditions, also, the *trans*-monotoluene-*p*-sulphonate (VI) was prepared from the *trans*-diol in 56% yield; for this derivative, however, the route *via* the oxide is more convenient. The *cis*-compound (XII) was characterised by conversion into the crystalline *cis*-ditoluene-*p*-sulphonate and *cis*-benzoate toluene-*p*-sulphonate.

*trans-cyclo*Pentane-1 : 2-diol monotoluene-*p*-sulphonate (VI) reacted readily with sodium iodide in boiling acetone, and a 46% yield of *trans*-2-iodo*cyclo*pentanol (IV) was obtained; the monomethanesulphonate behaved similarly. These results are in striking contrast to those obtained with the monosulphonates of *cyclo*hexane-1 : 2-diol (Clarke and Owen, *loc. cit.*), which required more vigorous treatment and gave only a very poor yield of 2-iodo-*cyclo*hexanol. Although unsaturated products were also formed in both series, the proportion of substitution to elimination is much greater with the *cyclo*pentane derivatives, though it is possible that this is due only to a difference in stability between the two iodohydrins.

Substitution by bromine was carried out by the use of lithium bromide in boiling ethanol. The *trans*-mono-methanesulphonate and -toluene-*p*-sulphonate gave *trans*-2-bromo*cyclo*-pentanol in 38% and 45% yield respectively. With boiling alcoholic lithium chloride the yields of *trans*-2-chloro*cyclo*pentanol were 50% and 56% respectively, slightly lower than those of *trans*-2-chloro*cyclo*hexanol from the corresponding *cyclo*hexane derivatives; the proportion of substitution product is therefore approximately the same in both series for this particular reagent. The *cis*-monotoluene-*p*-sulphonate (XII) also reacted with lithium chloride to give the *trans*-chlorohydrin (IV) and *cyclo*pentanone (XIII).

The steric results of these substitution reactions are the same as in the *cyclo*hexane series, and although Winstein and his collaborators have not studied any *cyclo*pentane compounds in their investigations of the neighbouring-group effect, it is very probable that their conclusions are equally applicable in this field. The retention of configuration in the reactions of the *trans*-monosulphonates of *cyclo*pentane-1 : 2-diol with halides can thus be

interpreted as resulting from two successive inversions, one at the formation of a cyclic intermediate (XIV) and the second on fission of this by reaction with halide ion. With the *cis*-compound (XII), bimolecular substitution occurs directly, with consequent inversion to give the *trans*-chlorohydrin. Further evidence for the applicability of Winstein's reasoning to *cyclo*pentane derivatives is afforded by the successful preparation of the *cis*-monoacetate (XI) referred to above.

The *trans*-ditoluene-*p*-sulphonate (VII) was largely unaffected by treatment for 48 hours with sodium iodide in boiling acetone or lithium chloride in boiling ethanol, though a little *cyclo*pentadiene (XV) was detected in the latter reaction. This low reactivity compared with that of the mono-derivative can be attributed to the strong deactivation produced on one group by the electron-attracting effect of the other (cf. Winstein, Grunwald, and Ingraham, *J. Amer. Chem. Soc.*, 1948, **70**, 821).

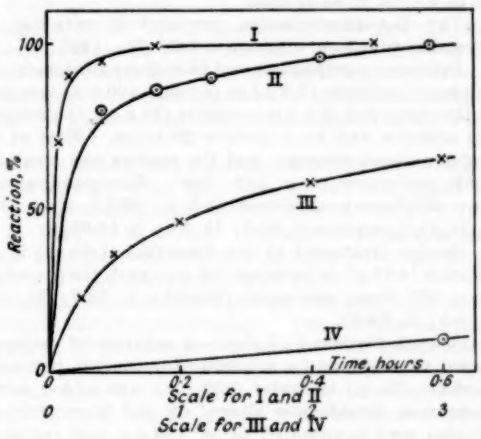
Reactions of the sulphonates with alkali were studied qualitatively and quantitatively. The *trans*-monotoluene-*p*-sulphonate (VI) with aqueous sodium hydroxide gave *cyclo*pentene oxide (III) which was further hydrolysed to the *trans*-diol (II). The *cis*-derivative (XII) gave *cyclo*pentanone. These results are similar to those observed with the monotoluene-*p*-sulphonates of *cyclo*hexane-1 : 2-diol, except that in the latter the *trans*-derivative

I, *Monotoluene*-p-*sulphonate of* trans-cyclo*pentane*-1 : 2-*diol* (0·005 *mol./l.*) *in* 0·01N-KOH–MeOH (20°).

II, *Monotoluene*-p-*sulphonate of* trans-cyclo*hexane*-1 : 2-*diol* (0·05 *mol./l.*) *in* 0·1N-KOH–MeOH (17°).

III, *Monotoluene*-p-*sulphonate of* cis-cyclo*pentane*-1 : 2-*diol* (0·05 *mol./l.*) *in* 0·1N-KOH–MeOH (20°).

IV, *Monotoluene*-p-*sulphonate of* cis-cyclo*hexane*-1 : 2-*diol* (0·05 *mol./l.*) *in* 0·1N-KOH–MeOH (17°).



also gave some *cyclo*pentylformaldehyde, formed by ring-contraction; no such by-product (*cyclo*butylformaldehyde) was encountered in the present case. The *trans*-ditoluene-*p*-sulphonate with methanolic potassium hydroxide gave *cyclo*pentadiene (XV) as the only recognisable product. Quantitative experiments clearly indicated the differences in rate of reaction between the *cis*- and the *trans*-monotoluene-*p*-sulphonates (see Fig.). At a concentration of only 0·005M in 0·01N-alcoholic potassium hydroxide at 20°, the *trans*-compound had reacted to the extent of over 90% in 3 minutes, whereas the *cis*-isomer in a solution ten times as concentrated underwent 36% reaction in 30 minutes. In such circumstances, accurate kinetic measurements for the *trans*-compound were not possible, but a rough estimate showed that the second-order velocity constant was about 800 times that of the *cis*-isomer. In 50% aqueous dioxan the reaction, as would be expected, was even faster, being complete with the *trans*-monotoluene-*p*-sulphonate within one minute; the *trans*-monomethanesulphonate behaved similarly. This difference in reactivity between *cis*- and *trans*-monotoluene-*p*-sulphonates has been previously encountered with the *cyclo*hexane-1 : 2-diol derivatives, and the reaction curves for these (taken from Part I) are included in the Figure. Consideration of these relative rates of reaction also shows that the *cyclo*pentane compounds are considerably more reactive than their *cyclo*hexane analogues. This provides a further illustration of the parallelism between toluene-*p*-sulphonates and halides, since Mousseron (*Bull. Soc. chim.*, 1946, 610) has found that the unimolecular

velocity constant for the solvolysis of *trans*-2-chloro*cyclo*pentanol is about 20 times greater than for *trans*-2-chloro*cyclo*hexanol. The same relative reactivity of the ring systems is also observed in the bimolecular reactions of *cyclo*pentyl and *cyclo*hexyl halides, and in the solvolysis of various alkyl*cyclo*pentyl and alkyl*cyclo*hexyl chlorides (Brown, Fletcher, and Johannesen, *J. Amer. Chem. Soc.*, 1951, **73**, 212; Brown and Borkowski, *ibid.*, 1952, **74**, 1894).

Experimental

*cyclo*Pentanone (*Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 192) was hydrogenated in alcoholic solution over Raney nickel at 70°/100 atm., to give *cyclo*pentanol (average yield, 75%). This was converted in 70% yield into *cyclo*pentene, b. p. 44—45°, by dehydration over phosphoric acid (*op. cit.*, Coll. Vol. II, p. 153).

trans-cyclo*Pentane*-1 : 2-*diol*.—A mixture of 30% aqueous hydrogen peroxide (13 g.) and formic acid (105 g.) was added to *cyclo*pentene (6·6 g.), much heat being generated. The temperature was allowed to fall to 40° and was so maintained for 4 hours. The formic acid was removed under reduced pressure, and the residue was dissolved in 10% aqueous sodium hydroxide (50 c.c.) and boiled under reflux for 45 minutes; water was then distilled off, and the residue twice distilled under reduced pressure, to give pure *trans-cyclo*pentane-1 : 2-diol (6 g., 60%), m. p. 50°, b. p. 93°/2 mm.

The di-*p*-nitrobenzoate, prepared in pyridine, had m. p. 140—141° (crude), raised on crystallisation from ethanol to 143° (lit., 145°).

Ditoluene-p-*sulphonate and Dimethanesulphonate of* trans-cyclo*Pentane*-1 : 2-*diol*.—Toluene-*p*-sulphonyl chloride (7·6 g.) in pyridine (20 c.c.) was added dropwise, during 1 hour, to a solution of the *trans*-diol (2 g.) in pyridine (20 c.c.), the temperature being kept at about 0° throughout the addition and for a further 20 hours. Most of the pyridine was then removed below 30° under reduced pressure, and the residue was treated with crushed ice, which precipitated the crude derivative, m. p. 103—104°. Recrystallisation from methanol gave colourless plates of pure *ditoluene*-p-*sulphonate* (5·3 g., 66%), m. p. 109° (Found: C, 55·4; H, 5·0; S, 15·6. $C_{19}H_{22}O_6S_2$ requires C, 55·6; H, 5·4; S, 15·6%).

Similar treatment of the *trans*-diol (1·85 g.) in pyridine (10 c.c.) with methanesulphonyl chloride (4·33 g.) in pyridine (10 c.c.) gave the *dimethanesulphonate* (3·90 g., 84%), small needles, m. p. 82° (from methanol) (Found: C, 32·7; H, 5·5; S, 24·8. $C_7H_{14}O_6S_2$ requires C, 32·6; H, 5·5; S, 24·8%).

cis-cyclo*Pentane*-1 : 2-*diol*.—A solution of *cyclo*pentene (21·8 g.) in ethanol (600 c.c.) was cooled to −40°, and a solution of potassium permanganate (40 g.) and anhydrous magnesium sulphate (30 g.) in water (800 c.c.) was added with vigorous stirring during 2 hours. The manganese dioxide was filtered off and thoroughly washed with hot water, and the combined filtrates were evaporated to *ca.* 100 c.c. and continuously extracted with ether for 48 hours. The dried ($MgSO_4$) extract was evaporated and distilled, to give *cis-cyclo*pentane-1 : 2-diol (11·1 g., 34%), b. p. 88—92°/2 mm., n_D^{21} 1·4770. The di-*p*-nitrobenzoate had m. p. 111—113° (crude), raised on crystallisation from ethanol to 117° (lit., 117—118°).

Ditoluene-p-*sulphonate and Dimethanesulphonate of* cis-cyclo*Pentane*-1 : 2-*diol*.—Toluene-*p*-sulphonyl chloride (5·3 g.) in pyridine (10 c.c.) was added to the *cis*-diol (1·4 g.) in pyridine (5 c.c.) at −10°, and the mixture was set aside at 0° overnight. The product was isolated as for the *trans*-compound described above; recrystallisation from methanol gave the cis-*ditoluene*-p-*sulphonate* as prisms (3·9 g., 69%), m. p. 92° (Found: C, 55·6; H, 5·1; S, 15·4%).

The cis-*dimethanesulphonate*, similarly prepared from *cis*-diol (1·15 g.) and methanesulphonyl chloride (2·7 g.) in pyridine (20 c.c.), crystallised from methanol in small plates (2·6 g., 89%), m. p. 82° (Found: C, 32·9; H, 5·7; S, 24·6%). A mixture with the *trans*-isomer, also of m. p. 82°, had m. p. *ca.* 64°.

2-*Chloro*cyclo*pentanol*.—Aqueous hypochlorous acid (*Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 158) was added dropwise with vigorous stirring to *cyclo*pentene (51 g.) in a 5-l. flask, maintained at 0°, until excess of hypochlorous acid was present. The product was steam-distilled from the aqueous suspension and extracted from the distillate with ether, to give 2-chloro*cyclo*pentanol (55·8 g., 61%), b. p. 88—90°/20 mm., n_D^{20} 1·4818. The procedure subsequently described in *Org. Synth.* (1950, **30**, 24) gives a yield of 52—56%.

Reduction of 2-*Chloro*cyclo*pentanone*.—Aluminium *iso*propoxide (20 g.) was dissolved in dry *iso*propyl alcohol (600 c.c.) and 2-chloro*cyclo*pentanone (16·5 g.) (Kötz, *Annalen*, 1913, **400**, 50) was added; the solution was heated on a steam-bath, and the acetone formed was removed by

fractionation through a 6″ Fenske column. The reaction mixture became dark red and some solid separated. After being heated for 3½ hours it was cooled, and dilute hydrochloric acid (35 c.c. of concentrated acid and 175 c.c. of water) was added. Extraction with ether gave a colourless liquid (6 g.), b. p. 57—65°/15 mm., n_D^{19} 1·4683, which reduced aqueous potassium permanganate, contained chlorine, and gave no ketonic reactions. The product (2 g.) was treated with 2N-sodium hydroxide (10 c.c.); heat was evolved, but after the suspension had been shaken for 12 hours no *cyclo*pentene oxide could be detected. The product (1 g.) from this hydrolysis was identified as a mixture of *cyclo*pentanol (phenylurethane, m. p. and mixed m. p. 132°) and *cyclo*pentanone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 144—145°).

cyclo*Pentene Oxide*.—Rothstein's method (*Compt. rend.*, 1936, **209**, 761), involving the treatment of 2-chloro*cyclo*pentanol with aqueous sodium hydroxide, gave an emulsion which was difficult to break; furthermore, the method involves extraction of the oxide with ether, in which it is very volatile, thus making separation on a small scale difficult. For the preparation of amounts up to 10 g. the following procedure was satisfactory.

A vigorously stirred mixture of 2-chloro*cyclo*pentanol (15 g.) and potassium hydroxide (45 g.) in water (16 c.c.) was gradually heated to 140° in an oil-bath, the product, together with some water, being condensed and collected. The lower, aqueous layer of the distillate was saturated with potassium carbonate, and the *cyclo*pentene oxide was separated, dried (K_2CO_3), and distilled, to give 5·4 g. (52%), b. p. 102°, n_D^{16} 1·4370.

Reaction of cyclo*Pentene Oxide with Hydrogen Halides*.—(i) *Hydrogen chloride*. *cyclo*Pentene oxide (3·8 g.) in dry ether (20 c.c.) was cooled to 0° and 1·5N-ethereal hydrogen chloride (35 c.c.) was added dropwise with cooling, the reaction being very vigorous. After 5 hours at 0°, the excess of hydrogen chloride was removed with water and then saturated aqueous sodium hydrogen carbonate; evaporation of the dried (Na_2SO_4) solution gave *trans*-2-chloro*cyclo*pentanol (3·8 g., 70%), b. p. 78°/15 mm., n_D^{16} 1·4808. It gave *cyclo*pentene oxide when treated with aqueous alkali as described above.

The product (0·5 g.) was treated in dry pyridine (5 c.c.) with *p*-nitrobenzoyl chloride (0·80 g.), to give trans-2-*chloro*cyclo*pentyl* p-*nitrobenzoate* (0·9 g., 80%), m. p. (crude) 76°, unchanged on recrystallisation from ethanol from which it formed colourless needles (Found: C, 53·7; H, 4·7; N, 5·2. $C_{12}H_{12}O_4NCl$ requires C, 53·4; H, 4·5; N, 5·2%). The chlorohydrin was also characterised as the *α-naphthylurethane* which after recrystallisation from light petroleum (b. p. 100—120°) had m. p. 105° (Found: N, 4·9. $C_{16}H_{16}O_3NCl$ requires N, 4·8%).

trans-2-*Chloro*cyclo*pentyl Acetate*.—*trans*-2-Chloro*cyclo*pentanol (2·8 g.) was kept with acetic anhydride (2·4 g.) in pyridine (20 c.c.) for 60 hours at room temperature. The solution was then diluted with water and extracted with chloroform. The extracts were washed with 2N-sulphuric acid (five times), water (once), and saturated aqueous sodium hydrogen carbonate (once), and after being dried (Na_2SO_4) and evaporated they gave trans-2-*chloro*cyclo*pentyl* acetate (2·7 g., 70%), b. p. 83°/15 mm., n_D^{15} 1·4563 (Found: C, 51·3; H, 6·5. $C_7H_{11}O_2Cl$ requires C, 51·7; H, 6·8%).

(ii) *Hydrogen bromide*. Dry hydrogen bromide was passed through a solution of *cyclo*pentene oxide (4·0 g.) in dry ether (30 c.c.), cooled to 0°, until no more was absorbed. The product was worked up as described above, to give *trans*-2-bromo*cyclo*pentanol (5·8 g., 73%), b. p. 92°/15 mm., n_D^{20} 1·5162.

The bromohydrin (0·7 g.) in pyridine (5 c.c.) with *p*-nitrobenzoyl chloride (0·8 g.) gave trans-2-*bromo*cyclo*pentyl* p-*nitrobenzoate*, which after two recrystallisations from ethanol formed fine needles, 1·1 g. (81%), m. p. 98° (Found: C, 46·1; H, 3·9; N, 4·4. $C_{12}H_{12}O_4NBr$ requires C, 45·9; H, 3·9; N, 4·5%).

(iii) *Hydrogen iodide*. Dry hydrogen iodide was passed into a cooled solution of *cyclo*pentene oxide (2·6 g.) in dry ether (20 c.c.); much heat was evolved and iodine was liberated. The solution was washed with aqueous sodium thiosulphate and with aqueous sodium hydrogen carbonate, and evaporated, to give *trans*-2-iodo*cyclo*pentanol (1·5 g., 23%), b. p. 55—58°/0·2 mm., n_D^{20} 1·5670, as a yellow liquid, which gave the strong characteristic odour of *cyclo*pentene oxide when treated with aqueous silver nitrate.

Treatment of the iodohydrin (0·9 g.) in pyridine (5 c.c.) with *p*-nitrobenzoyl chloride (0·87 g.) gave trans-2-*iodo*cyclo*pentyl* p-*nitrobenzoate*, which crystallised from ethanol in plates (1·2 g., 80%), m. p. 108° (Found: C, 40·0; H, 3·4; N, 3·7. $C_{12}H_{12}O_4NI$ requires C, 39·9; H, 3·4; N, 3·9%).

Monoacetate of trans-cyclo*Pentane*-1 : 2-*diol*.—(i) Acetic acid did not react at room temperature with *cyclo*pentene oxide either in the absence of any other solvent or in ether, with or without a trace of concentrated sulphuric acid. Reaction occurred, however, when the oxide

(2·9 g.) was heated with glacial acetic acid (5 c.c.) at 100° for 15 hours. The excess of acid and unchanged oxide were distilled off, and the residue was distilled, to give the *monoacetate* (2·03 g., 40%), b. p. 93—97°/20 mm., n_D^{20} 1·4553 (Found: C, 58·3; H, 8·5. $C_7H_{12}O_3$ requires C, 58·3; H, 8·4%).

Treatment of a portion of this product with *p*-nitrobenzoyl chloride in pyridine gave the *acetate* p-*nitrobenzoate* of *trans-cyclo*pentane-1 : 2-diol, which crystallised from ethanol in microscopic needles, m. p. 80—81° (Found: C, 57·7; H, 5·2; N, 4·8. $C_{14}H_{15}O_6N$ requires C, 57·3; H, 5·2; N, 4·8%).

(ii) *cyclo*Pentene (5 g.) was slowly added, with cooling, to a solution containing peracetic acid, prepared from glacial acetic acid (35 g.) and 30% aqueous hydrogen peroxide (8 g.). After 16 hours at room temperature, the solution (which still had an odour of *cyclo*pentene) was carefully neutralised with aqueous sodium hydroxide, with cooling, and extracted with ether, to give the *trans*-monoacetate (1·8 g., 17%), b. p. 60—64°/0·2 mm., n_D^{23} 1·4575 (Found: sap. equiv., 147. Calc. for $C_7H_{12}O_3$: equiv., 144).

Monotoluene-p-*sulphonate of* trans-cyclo*Pentane*-1 : 2-*diol*.—A solution of *cyclo*pentene oxide (10 g.) in anhydrous ether (50 c.c.) was slowly added to a suspension of dry toluene-*p*-sulphonic acid (21 g.) in anhydrous ether (50 c.c.) at 0°; the acid dissolved during the addition. The solution was left for 16 hours at room temperature, and was then washed with water, dried (Na_2SO_4), and evaporated, finally at 0·2 mm., to give the *monotoluene*-p-*sulphonate* of *trans-cyclo*pentane-1 : 2-diol (21 g., 69%), n_D^{23} 1·5280 (Found: S, 11·9. $C_{12}H_{16}O_4S$ requires S, 12·5%), as a pale yellow viscous liquid. On treatment with toluene-*p*-sulphonyl chloride in pyridine it gave the *trans*-ditoluene-*p*-sulphonate, m. p. and mixed m. p. 109°.

The trans-*benzoate toluene*-p-*sulphonate*, prepared in 67% yield by reaction of the monotoluene-*p*-sulphonate (1 g.) with benzoyl chloride (0·55 g.) in pyridine (10 c.c.), crystallised from methanol in long needles, m. p. 113—114° (Found: C, 63·2; H, 5·7; S, 8·8. $C_{19}H_{20}O_5S$ requires C, 63·3; H, 5·6; S, 8·9%).

Treatment of the monotoluene-*p*-sulphonate (0·63 g.) in pyridine (3 c.c.) with methanesulphonyl chloride (0·28 g.) for 2 hours at 0°, followed by dilution with water, precipitated the trans-*methanesulphonate toluene*-p-*sulphonate* (0·60 g., 73%), m. p. 72—74°, which crystallised from methanol, with almost quantitative recovery, in small prisms, m. p. 75° (Found: C, 46·7; H, 5·3; S, 18·9. $C_{13}H_{18}O_6S_2$ requires C, 46·7; H, 5·3; S, 19·2%).

Monomethanesulphonate of trans-cyclo*Pentane*-1 : 2-*diol*.—*cyclo*Pentene oxide (12 g.) in anhydrous ether (25 c.c.) was added slowly to a stirred solution of methanesulphonic acid (13·5 g.) in dry ether (50 c.c.) at 0°. The solution was kept for 16 hours at 0° and then worked up as for the similar reaction with toluene-*p*-sulphonic acid, to give the crude *trans*-monomethanesulphonate as a pale yellow liquid (15·2 g., 59%), n_D^{22} 1·4730 (Found: S, 13·7. Calc. for $C_6H_{12}O_4S$: S, 17·8%). Owing to its high reactivity, some decomposition had probably occurred during the work up. It was characterised by reaction with methanesulphonyl chloride in pyridine, to give the *trans*-dimethanesulphonate, m. p. and mixed m. p. 82°, and by conversion with toluene-*p*-sulphonyl chloride in pyridine into the *trans*-methanesulphonate toluene-*p*-sulphonate, identical (m. p. and mixed m. p. 75°) with that prepared from the monotoluene-*p*-sulphonate.

Monoacetate of cis-cyclo*Pentane*-1 : 2-*diol*.—To a solution of the *trans*-monotoluene-*p*-sulphonate (6 g.) in pyridine (50 c.c.), acetic anhydride (2·5 g.) was added, with cooling. After 24 hours at room temperature, water (100 c.c.) was added, and the solution was extracted with chloroform. The extract was washed successively with dilute sulphuric acid, water, and saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated, to give the crude *trans*-acetate toluene-*p*-sulphonate (5·8 g.). This product (5·0 g.), fused potassium acetate (8 g.), and dry ethanol (75 c.c.) were boiled under reflux for 24 hours. The solution was then cooled, filtered from potassium salts, and evaporated to dryness under reduced pressure. Extraction of the residue with ether gave the *monoacetate* of *cis-cyclo*pentane-1 : 2-diol (1·25 g., 44%), b. p. 104—106°/20 mm., n_D^{17} 1·4576 (Found: C, 58·3; H, 8·6. $C_7H_{12}O_3$ requires C, 58·3; H, 8·4%). With *p*-nitrobenzoyl chloride in pyridine it gave the cis-*acetate* p-*nitrobenzoate*, which crystallised from ethanol in white nodules, m. p. 93—94° (Found: N, 4·8. $C_{14}H_{15}O_6N$ requires N, 4·8%). The m. p. was depressed on admixture with the *trans*-acetate *p*-nitrobenzoate.

The monoacetate (0·71 g.) was dissolved in dry methanol (50 c.c.) containing a trace of sodium and set aside for 16 hours. After the addition of a few drops of water, the solution was neutralised with carbon dioxide and evaporated to an oil, which was taken up in dry ether and filtered to remove sodium carbonate. Evaporation then gave *cis-cyclo*pentane-1 : 2-diol (0·3 g.),

which was characterised by conversion into the ditoluene-*p*-sulphonate; one recrystallisation from methanol gave 0·93 g. (75%), m. p. 90—92°, raised on further recrystallisation to 92°, undepressed on admixture with the *cis*-derivative previously described.

Monotoluene-p-*sulphonate of* cis-cyclo*Pentane*-1 : 2-*diol*.—To a solution of *cis-cyclo*pentane-1 : 2-diol (3·8 g.) in dry pyridine (75 c.c.), maintained at −10°, a solution of toluene-*p*-sulphonyl chloride (7·0 g.) in chloroform (75 c.c.) was gradually added with stirring over a period of three days (during the nights the mixture was stored at *ca.* 0°). After a further day at 0°, most of the solvent was removed under reduced pressure below 30° and the residue was diluted with water (100 c.c.). The precipitated oil was taken up in chloroform (80 c.c.), and washed with dilute sulphuric acid, water, and sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) solution, finally at 0·2 mm., gave the cis-*monotoluene*-p-*sulphonate* as a pale yellow oil (3·8 g., 40%), n_D^{23} 1·5290 (Found: S, 12·7. $C_{12}H_{14}O_4S$ requires S, 12·5%). The product was completely soluble in cold methanol, and therefore contained no appreciable amount of ditoluene-*p*-sulphonate. Treatment of a portion with toluene-*p*-sulphonyl chloride in pyridine gave the *cis*-ditoluene-*p*-sulphonate, m. p. and mixed m. p. 92°.

The cis-*benzoate toluene*-p-*sulphonate* was prepared by reaction of the *cis*-monotoluene-*p*-sulphonate (0·5 g.) with benzoyl chloride (0·27 g.) in pyridine (5 c.c.). Three recrystallisations of the product from methanol gave small needles (0·23 g.), m. p. 92—93° (Found: C, 63·3; H, 5·7; S, 9·0. $C_{19}H_{20}O_5S$ requires C, 63·3; H, 5·6; S, 8·9%).

Reactions of the Monotoluene-p-*sulphonate and Monomethanesulphonate of* trans-cyclo*Pentane*-1 : 2-*diol with Metal Salts*.—(a) *Sodium iodide*. (i) A solution of the monotoluene-*p*-sulphonate (6·0 g.) and sodium iodide (9·5 g.) in pure acetone (70 c.c.) was boiled under reflux for 4 hours; some iodine was formed, and sodium toluene-*p*-sulphonate (3·5 g., 77%) was deposited. The solid was removed and the bulk of the acetone was distilled off, the distillate being unsaturated to bromine in carbon tetrachloride. Water (20 c.c.) was added to the residue, which was then extracted with ether. The ethereal extracts were washed with aqueous sodium thiosulphate, dried (Na_2SO_4), and evaporated to an oil, which on distillation gave *trans*-2-iodo*cyclo*pentanol (2·35 g., 46%), b. p. 95—97°/1·5 mm., n_D^{20} 1·5647. This was characterised by conversion of a portion into *trans*-2-iodo*cyclo*pentyl *p*-nitrobenzoate which when recrystallised from ethanol had m. p. and mixed m. p. 108°.

(ii) When the reaction period was increased to 24 hours, the theoretical amount of sodium toluene-*p*-sulphonate was deposited but considerably more iodine was liberated. The yield of *trans*-2-iodo*cyclo*pentanol fell to 26% and a lower-boiling fraction of *cyclo*pentanone was isolated and characterised as the 2 : 4-dinitrophenylhydrazone, m. p. 143°.

(iii) Treatment of the monomethanesulphonate (3·95 g.) with sodium iodide (8·5 g.) in boiling acetone (60 c.c.) for 5 hours gave sodium methanesulphonate (2·4 g.) and *trans*-2-iodo*cyclo*pentanol (2·2 g., 47%), b. p. 54°/0·1 mm., n_D^{16} 1·5638. The latter was not quite pure, as indicated by the slightly low refractive index and by the semi-solid nature of the crude *p*-nitrobenzoate; recrystallisation of the latter, however, gave the pure derivative, m. p. and mixed m. p. 108°.

(b) *Lithium bromide*. (i) The monotoluene-*p*-sulphonate (5 g.) and lithium bromide (5·6 g.) in dry ethanol (40 c.c.) were boiled under reflux for 24 hours. The solvent was removed under reduced pressure and water (30 c.c.) was added to the yellow residue, which was then extracted with ether. Evaporation of the dried (Na_2SO_4) extracts gave *trans*-2-bromo*cyclo*pentanol (1·45 g., 45%), b. p. 92—93°/15 mm., n_D^{18} 1·4990, characterised as *trans*-2-bromo*cyclo*pentyl *p*-nitrobenzoate, m. p. and mixed m. p. 98°, after recrystallisation from ethanol.

(ii) Treatment of the monomethanesulphonate (3·0 g.) with lithium bromide (4·5 g.) in dry ethanol (30 c.c.) in a similar way gave *trans*-2-bromo*cyclo*pentanol (1·05 g., 38%), b. p. 92—94°/15 mm., n_D^{18} 1·5015, which was again characterised as the *p*-nitrobenzoate, m. p. and mixed m. p. 98°.

(c) *Lithium chloride*. (i) A solution of the monotoluene-*p*-sulphonate (6·2 g.) and dry lithium chloride (3·5 g.) in dry ethanol (25 c.c.) was boiled under reflux for 24 hours, the solution remaining colourless throughout. The ethanol was distilled off and the residue diluted with water (30 c.c.). The product was extracted with chloroform, and the extract was dried (Na_2SO_4) and evaporated to a residue which when distilled gave *trans*-2-chloro*cyclo*pentanol (1·93 g., 66%), b. p. 80—82°/16 mm., n_D^{23} 1·4767; reaction of a portion with *p*-nitrobenzoyl chloride in pyridine gave *trans*-2-chloro*cyclo*pentyl *p*-nitrobenzoate, m. p. and mixed m. p. 76°.

(ii) Similarly, treatment of the monomethanesulphonate (3·0 g.) with lithium chloride (2·5 g.) in boiling ethanol (20 c.c.) for 24 hours gave *trans*-2-chloro*cyclo*pentanol (1 g., 50%), b. p. 75—77°/10 mm., n_D^{16} 1·4786; the *p*-nitrobenzoate had m. p. and mixed m. p. 76°.

*Reaction of the Monotoluene-*p*-sulphonate of* cis-cyclo*Pentane*-1 : 2-*diol with Lithium Chloride.*—The *cis*-monotoluene-*p*-sulphonate (2·6 g.) in dry ethanol (35 c.c.) was boiled under reflux with lithium chloride (1·5 g.) for 24 hours. The solution was then concentrated, diluted with water, and extracted with ether, to give an oil which on distillation was separated into fractions (i) (0·17 g.), b. p. 50°/100 mm., n_D^{27} 1·3742, and (ii) (0·17 g.), b. p. 90—95°/25 mm., n_D^{27} 1·4663. The former contained no chlorine and when treated with aqueous 2 : 4-dinitrophenylhydrazine sulphate gave *cyclo*pentanone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 144°. Fraction (ii) was treated with *p*-nitrobenzoyl chloride (0·2 g.) in pyridine (2 c.c.) to give, after 3 recrystallisations from ethanol, *trans*-2-chloro*cyclo*pentyl *p*-nitrobenzoate, m. p. and mixed m. p. 76°.

*Reactions of the Ditoluene-*p*-sulphonate of* trans-cyclo*Pentane*-1 : 2-*diol with Metal Salts.*—(a) *Sodium iodide.* The *trans*-ditoluene-*p*-sulphonate (1·4 g.) and sodium iodide (4 g.) in acetone (50 c.c.) were heated under reflux for 48 hours. The iodine which had been formed was removed by the addition of aqueous sodium thiosulphate (the amount required indicated the presence of 0·3 atomic proportion of iodine), and the acetone was distilled off. Dilution of the residue with water precipitated unchanged ditoluene-*p*-sulphonate (1·1 g., 79%).

(b) *Lithium chloride.* A solution of the *trans*-ditoluene-*p*-sulphonate (2·5 g.) and lithium chloride (2·5 g.) in dry ethanol (25 c.c.) was boiled under reflux for 40 hours. The colourless solution was concentrated to remove acetone and then diluted with water; unchanged ditoluene-*p*-sulphonate (1·4 g., 56%) was precipitated. Extraction of the filtrate with ether gave only a trace of a chlorine-containing oil.

*Alkaline Hydrolysis of the Toluene-*p*-sulphonates.*—(a) *Qualitative.* (i) A suspension of the *trans*-monotoluene-*p*-sulphonate (7 g.) in 0·5N-aqueous sodium hydroxide (60 c.c.) was rapidly stirred at 85—90°; the characteristic odour of *cyclo*pentene oxide was soon apparent. After 2 hours the solution became homogeneous, and it was cooled, extracted once with chloroform to remove any unchanged toluene-*p*-sulphonate, and then continuously extracted with ether for 2 days. Evaporation of the dried (Na_2SO_4) ethereal extracts gave an oil, from which *trans-cyclo*pentane-1 : 2-diol (0·73 g., 26%), b. p. 82°/0·2 mm., was obtained by distillation. It was characterised by conversion into the *trans*-ditoluene-*p*-sulphonate, m. p. and mixed m. p. 109°. The poor yield of diol was probably due to loss of the volatile *cyclo*pentene oxide.

(ii) The *cis*-monotoluene-*p*-sulphonate (0·6 g.) was dissolved on 0·6N-methanolic sodium methoxide (4 c.c.); the solution became hot and sodium toluene-*p*-sulphonate was precipitated. A few drops of water were added, and the excess of alkali was neutralised with carbon dioxide. The solution was filtered, acidified with sulphuric acid, and treated with aqueous 2 : 4-dinitrophenylhydrazine sulphate, to give a yellow precipitate which was purified by chromatography from benzene solution on alumina; recrystallisation from ethanol then gave *cyclo*pentanone 2 : 4-dinitrophenylhydrazone (0·11 g.), m. p. and mixed m. p. 144°.

(iii) A solution of the *trans*-ditoluene-*p*-sulphonate (0·2 g.) in N-methanolic potassium hydroxide (12 c.c.) was boiled under reflux for 20 hours, *cyclo*pentadiene being formed [the diene is conveniently detected by passage of a slow stream of nitrogen through the apparatus and thence through a solution of sodium nitroprusside in 1% methanolic potassium hydroxide, a red precipitate being formed (Scagliarini and Lucchi, *Chem. Abs.*, 1940, **34**, 2287)]. The precipitated potassium toluene-*p*-sulphonate (0·17 g., 85%) was removed, and the solution was concentrated to remove methanol, and then diluted with water and continuously extracted with ether for 24 hours; evaporation of the extracts gave no residue.

(b) *Quantitative.* (i) The *trans*-monotoluene-*p*-sulphonate (0·2786 g.) was diluted with methanol to 100 c.c., to give a 0·0109M-solution. A portion (10 c.c.) was quickly mixed with 0·0232N-methanolic potassium hydroxide (10 c.c.) and kept at 20° for a known time before the rapid addition of 0·02N-aqueous hydrochloric acid (10 c.c.). The excess of acid was estimated by back-titration, and the percentage reaction of the toluene-*p*-sulphonate was then calculated. The results are shown in the Figure. The second-order velocity coefficient decreased markedly as the reaction proceeded; extrapolation to zero time gave the value $k_2 = 140$ mole $l.^{-1}$ $min.^{-1}$. Owing to the high rate, the possible experimental error is considerable, and this result can be regarded only as being of the correct order of magnitude.

(ii) The *cis*-monotoluene-*p*-sulphonate (2·25 g.) was diluted with methanol to 100 c.c., to give a 0·0879M-solution. Reactions were carried out, as described above, with equal volumes of 0·2384N-methanolic potassium hydroxide. The results are shown in the Figure. Second-order velocity coefficients again showed a decrease with time. Extrapolation to zero gave $k_2 = 0{\cdot}17$ mole $l.^{-1}$ $min.^{-1}$.

(iii) When an approximately 0·0100M-solution of either the *trans*-monotoluene-*p*-sulphonate

or *trans*-monomethanesulphonate in dioxan was treated with an equal volume of 0·0246N-aqueous sodium hydroxide at 20°, complete reaction had occurred when the first measurement was made (1 minute).

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771. *Alicyclic Glycols. Part VII.** cyclo*Pentane*-1 : 3-*diol. Anionotropic Rearrangement in Some Reactions of* 3 : 5-*Dibromo*cyclo*pentene.*

By L. N. OWEN and PETER N. SMITH.

A re-investigation of the methods used by earlier workers for the synthesis of *cyclo*pentane-1 : 3-diol has shown that in all cases the products contain considerable proportions of *cyclo*pentane-1 : 2-diol.

Replacement of bromine by acetoxyl in *cis*- and in *trans*-3 : 5-dibromo-*cyclo*pentene (VIII) has been studied under various conditions. When potassium acetate or silver acetate in acetic acid is used, the normal product, 3 : 5-diacetoxy*cyclo*pentene, is accompanied by 3 : 4-diacetoxy*cyclo*pentene, formed by anionotropic rearrangement; the configuration of the rearranged product is *cis* if the reaction is carried out in the presence of water, but *trans* if anhydrous acetic acid is used, irrespective of the configuration of the original dibromide. This can be explained by the assumption that the anionotropic change occurs when the first bromine atom is replaced, to give *trans*-3-acetoxy-4-bromo*cyclo*pentene (X), which then forms a cyclic intermediate (XI) of the Winstein type. When the dibromide reacts with tetraethylammonium acetate in acetone, rearrangement does not occur, and deacetylation and hydrogenation of the product gives only *cyclo*pentane-1 : 3-diol; in this way the pure *cis*- and *trans*-forms have been prepared for the first time.

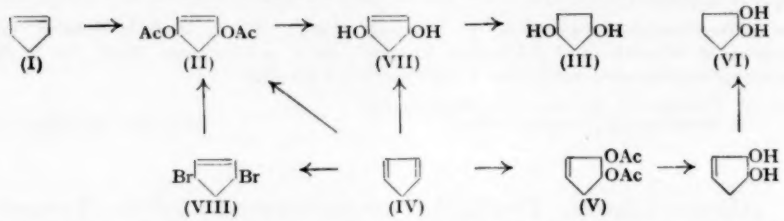
The ditoluene-*p*-sulphonate of *trans-cyclo*pentane-1 : 3-diol reacts readily with potassium acetate, potassium *p*-nitrobenzoate, or sodium iodide, to give the corresponding 1 : 3-*trans*-derivatives; although some *cyclo*pentadiene is also formed the proportion of substitution to elimination is greater than for any other alicyclic toluene-*p*-sulphonate. The dimethanesulphonate with aqueous alkali gives *cyclo*pent-2-enol. The monotoluene-*p*-sulphonate of *trans-cyclo*pentane-1 : 3-diol shows very low reactivity in comparison with the corresponding 1 : 2-compound.

IN contrast to the *cyclo*pentane-1 : 2-diols, the two stereoisomers of which have been known and studied for many years (cf. preceding paper), comparatively little is known about the *cyclo*pentane-1 : 3-diols, and the available information is in many respects of doubtful accuracy.

Dane, Schmitt, and Rautenstrauch (*Annalen*, 1937, **532**, 29) oxidised *cyclo*pentene (I) with selenium dioxide in acetic anhydride and obtained a mixture of mono- and di-acetoxy*cyclo*pentene; deacetylation and hydrogenation of the supposed di-ester (II) gave a product (bisphenylurethane, m. p. 195°) which should evidently be a *cyclo*pentane-1 : 3-diol (III). Criegee and Beucker (*ibid.*, 1939, **541**, 218), by oxidation of *cyclo*pentadiene (IV) with phenyl iodosoacetate in acetic acid, obtained a mixture of 3 : 4- (V) and 3 : 5-diacetoxy-*cyclo*pentene (II), which was hydrolysed and hydrogenated to give a mixture of almost equal parts of *cyclo*pentane-1 : 2- and -1 : 3-diol; the 1 : 2-diol (VI) was destroyed with lead tetra-acetate, and the remaining 1 : 3-diol (III) was shown to be a mixture of stereoisomers by conversion into two bisphenylurethanes, m. p.s 173° and 145° respectively. Milas and Maloney (*J. Amer. Chem. Soc.*, 1940, **62**, 1841) treated *cyclo*pentadiene with hydrogen peroxide in dry *tert.*-butyl alcohol in the presence of osmic acid, and isolated a product,

* Part VI, preceding paper.

formulated as *cis-cyclo*pent-2-ene-1 : 4-diol (VII), which on hydrogenation was said to give a *cyclo*pentane-1 : 3-diol, the bisphenylurethane of which had m. p. 168—171°.



Blomquist and Mayes (*J. Org. Chem.*, 1945, **10**, 134) treated *cis*-3 : 5-dibromo*cyclo*pentene (VIII) with potassium acetate in acetic acid and isolated an unsaturated diacetate, assumed to be *cis*-(II), which on deacetylation and hydrogenation gave a *cyclo*pentanediol (bisphenylurethane, m. p. 171°). Similar reaction of the *trans*-dibromide, but with silver acetate in acetic acid, likewise gave an unsaturated diacetate, deacetylation and hydrogenation of which gave another *cyclo*pentanediol (bisphenylurethane, m. p. 184°) in very poor yield. Both diols were assumed to be 1 : 3-compounds, and to have been formed with overall retention of configuration.

Consideration of the melting points of the bisphenylurethanes of the alleged 1 : 3-diols reported by these various investigators shows that four different values are recorded, even on the assumption that those of m. p. 168—171°, 171°, and 173° are essentially identical with one another. A complete re-investigation of the problem was therefore undertaken.

Repetition of the procedure of Dane *et al.* gave the unsaturated diacetate in improved yield. The saturated diol prepared from this material reacted to the extent of 64% with aqueous sodium metaperiodate, thus showing it to be a mixture of 1 : 2- and 1 : 3-diols, and not, as claimed, a pure 1 : 3-compound. When the method of Milas and Maloney was used, the saturated product contained 53% of 1 : 2-diol; the preparation was undertaken thrice, with the same result, and the non-reactivity towards lead tetra-acetate claimed by Milas and Maloney is inexplicable. Their reported formation of a benzylidene derivative cannot, of course, be taken as evidence that no 1 : 2-diol was present.

The work of Blomquist and Mayes was then repeated, *cis*-3 : 5-dibromo*cyclo*pentene being prepared from *cyclo*pentadiene in improved yield (over 80%). Reaction with potassium acetate in acetic acid gave an unsaturated diacetate which on deacetylation and hydrogenation furnished a *cyclo*pentanediol; this by periodate titration was found to contain 63% of the 1 : 2-isomer, confirmed by toluene-*p*-sulphonation, and isolation of the crystalline ditoluene-*p*-sulphonate of *trans-cyclo*pentane-1 : 2-diol (cf. Part VI, previous paper). By using the crude *cis*-dibromide in the replacement reaction the overall yield of unsaturated diacetate was raised to 63% (cf. 14% by Blomquist and Mayes on the two stages).

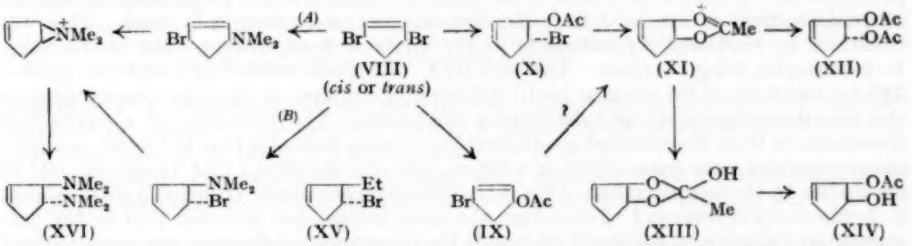
Reaction of the *trans*-dibromide with silver acetate in acetic acid, followed by deacetylation and hydrogenation of the product, gave a diol *which consisted almost entirely* (93%) *of* 1 : 2-*compound* and which readily gave the di-*p*-nitrobenzoate of *cis-cyclo*pentane-1 : 2-diol. Since this derivative is the most soluble of all the di-*p*-nitrobenzoates of the isomeric *cyclo*pentanediols (cf. previous paper for the 1 : 2-series; the authentic 1 : 3-compounds are described below) the diol must have been nearly pure *cis*-1 : 2-isomer.

It has thus been found that all earlier methods for the preparation of *cyclo*pentane-1 : 3-diol give mixtures, most of which are actually richer in the 1 : 2-isomer. Whilst the 1 : 2-diol formed in the hydroxylation of *cyclo*pentadiene may arise by direct 1 : 2-addition, its formation in Dane's method or from the 1 : 3-dibromides must involve rearrangement. In the investigation of Blomquist and Mayes's route, the deacetylation and hydrogenation stages were interchanged without appreciable effect on the proportions of 1 : 2- and 1 : 3-diols encountered in the final product, and there can be no doubt that the 1 : 2-compound must be formed by anionotropic rearrangement during the conversion of the dibromides

into the unsaturated diacetates. Since completion of this work, the formation of 1 : 2-compounds from 3 : 5-dibromo*cyclo*pentene has been reported in its reactions with ethylmagnesium bromide (Barber and English, *J. Amer. Chem. Soc.*, 1951, **73**, 746) and with dimethylamine (Cope, Estes, Emery, and Haven, *ibid.*, p. 1199; see also Ried and Yost, *ibid.*, 1950, **72**, 1807).

The fact that the 1 : 2-diol formed in our experiments was *cis* from the *trans*-1 : 4-dibromide, and *vice versa*, showed that there was a marked stereochemical specificity in the rearrangement, which apparently resulted in overall inversion. However, in these experiments it so happened that the reaction of the *cis*-dibromide with potassium acetate in acetic acid was carried out in the presence of some acetic anhydride, *i.e.*, under anhydrous conditions, whereas interaction of the *trans*-dibromide with silver acetate was done in ordinary acetic acid without exclusion of moisture. Further experiments were therefore carried out, as follows. Treatment of the *cis*-dibromide with silver acetate in *moist* acetic acid, followed by the usual deacetylation and hydrogenation, gave a product which contained 81% of 1 : 2-diol and readily gave derivatives of *cis-cyclo*pentane-1 : 2-diol; *i.e.*, the configuration was the opposite of that found under the original dry conditions. Furthermore, the *trans*-dibromide, with silver acetate in *dry* acetic acid, gave a product (containing 42% of 1 : 2-diol) which by fractional crystallisation of the ditoluene-*p*-sulphonates was shown to include *trans*-1 : 2-, *cis*-1 : 3-, and *trans*-1 : 3-*cyclo*pentanediols; owing to the practical difficulties involved in the separation of these three stereoisomers, it cannot be claimed, though it is very probable, that the *cis*-1 : 2-compound was entirely absent, but there is no doubt that the 1 : 2-diol produced was mainly the *trans*-form. It is therefore established that *irrespective of the configuration of the dibromide* the *cis*-1 : 2-diol is formed when water is present, and the *trans*-1 : 2-diol under anhydrous conditions.

There are two possible ways in which the 1 : 2-product can be formed, depending upon the stage at which rearrangement occurs, and the intermediate can be either 3-acetoxy-5-bromo- (IX) or 3-acetoxy-4-bromo-*cyclo*pentene (X). The dependence of the configuration of the 1 : 2-diol on the presence or absence of water suggests the operation of a mechanism similar to that proposed by Winstein and Buckles (*ibid.*, 1942, **64**, 2780, 2787) to explain the formation of either *cis*- or *trans*-derivatives of *cyclo*hexane-1 : 2-diol, in wet or dry acetic acid respectively, from *trans*-1-acetoxy-2-bromo*cyclo*hexane and silver acetate. Evidence



for the applicability of Winstein's reasoning to the *cyclo*pentane field has been presented in Part VI (preceding paper), and in the present instance a cyclic intermediate (XI) in dry acetic acid would undergo acetolysis with inversion to give the *trans*-diacetate (XII), whereas in the presence of water the formation of the orthoacetate (XIII) would lead to the *cis*-monoacetate (XIV), and, by further esterification, to the *cis*-diacetate. If (XI) is derived from (X), the latter must have the *trans*-configuration shown in order that cyclisation can be accompanied by the usual inversion on the carbon atom carrying the halogen, and it seems likely that an anionotropic rearrangement (VIII) ⟶ (X) might give a *trans*-product preferentially (from either *cis*- or *trans*-dibromide) because of steric hindrance by the remaining bromine atom, which would lead to opposite-side attack on the adjacent carbon atom. This is supported by the important observation by Barber and English (*loc. cit.*), for which they offer a similar explanation, that either *cis*- or *trans*-(VIII) with ethylmagnesium bromide gives a 4-bromo-3-ethyl*cyclo*pentene which is almost certainly the *trans*-compound (XV). The possible formation of (XI) by the other route, from (IX), is a

type of reaction for which no analogy appears to exist, but if it occurs it would probably be independent of the configuration of (IX) and hence of the original dibromide. In the absence of further evidence, however, we regard the route (VIII) ⟶ (X) as the more probable. In this connection it may be pointed out that the formation of *trans*-3 : 4-bisdimethylamino*cyclo*pentene (XVI) from both *cis*- and *trans*-(VIII) could be explained not only by the mechanism (*A*) suggested by Cope *et al.* (*loc. cit.*), but by the alternative (*B*).

Roberts, Young, and Winstein (*ibid.*, p. 2157), in their studies on the replacement reactions of the butenyl chlorides, found that anionotropic rearrangement was inhibited in non-hydroxylic solvents (cf. Steigmann and Hammett, *ibid.*, 1937, **59**, 2536) and that with potassium acetate in acetic anhydride, or tetraethylammonium acetate in acetone, reaction occurred exclusively by the S_N2 mechanism to give the normal acetates. In our own experiments, described above, it had been observed that the proportion of 1 : 2-diol was less in those reactions when dry acetic acid had been used, and it was found that when *trans*-3 : 5-dibromo*cyclo*pentene was treated with potassium acetate in boiling acetic anhydride the product, after the usual deacetylation and hydrogenation, contained only 26% of 1 : 2-diol. Even better results were obtained with tetraethylammonium acetate in acetone; the *trans*-dibromide reacted very smoothly, the replacement of halogen, even at 0°, being complete in an hour [this illustrates the high reactivity of the dibromide compared with that of 1-methylallyl chloride towards the same reagent, for which 7 days at reflux temperature were required for complete reaction (Roberts, Young, and Winstein, *loc. cit.*)]. The resulting unsaturated diacetate was deactylated and hydrogenated, to give a pure *cyclo*pentane-1 : 3-diol, m. p. 40°, which was quite free from 1 : 2-diol. This process therefore represents the first satisfactory method for the synthesis of this elusive compound. The evidence for the allocation of the *trans*-configuration to the solid 3 : 5-dibromide by Thiele (*Annalen*, 1900, **314**, 296) appears to be sound, and on the usual assumption that bimolecular replacement of each halogen atom occurs with inversion the resulting 1 : 3-diol can be assigned the *trans*-structure. It gave a bisphenylurethane the m. p. (162—163°) of which was different from all the alleged 1 : 3-derivatives referred to earlier. The crystalline di-*p*-nitrobenzoate, dimethanesulphonate, and ditoluene-*p*-sulphonate were also prepared.

Similar treatment of the *cis*-dibromide gave a liquid *cyclo*pentane-1 : 3-diol which also was free from any 1 : 2-isomer. It gave a bisphenylurethane, m. p. 172°, but in rather poor yield, and from the behaviour of the products isolated in the preparation of this and other derivatives it appeared that the diol was not stereochemically pure. This was confirmed by fractional crystallisation of the ditoluene-*p*-sulphonate, some of the *trans*-1 : 3-derivative being obtained. The pure *cis*-1 : 3-diol was isolated as a solid, m. p. 30—32°, by solvolysis of the purified *cis*-1 : 3-di-*p*-nitrobenzoate; it was also characterised as the dimethanesulphonate and ditoluene-*p*-sulphonate. The formation of a mixture of stereoisomers from the so-called *cis*-dibromide probably indicates that the latter, a liquid, always contains some *trans*-isomer in solution, and it is significant that Thiele (*loc. cit.*) in his studies on the configurations of the 3 : 5-dibromo*cyclo*pentenes obtained a good yield of 3 : 5-dibromo*cyclo*pentane-1 : 2-diol from the solid isomer, but reported that in the permanganate oxidation of the liquid dibromide the dibromoglycol obtained was contaminated with the stereoisomeric compound derived from the *trans*-dibromide.

It is of interest that, in those cases mentioned earlier when appreciable amounts of 1 : 2-diol were produced, the 1 : 3-diol formed usually contained both stereosiomers even when the pure *trans*-dibromide had been used. This suggests that the normal replacement reaction (without rearrangement) occurs partly by a S_N1 mechanism in the more highly ionising solvents.

One additional route to the *cyclo*pentane-1 : 3-diols was investigated, following the report of Mugdan and Young (*J.*, 1949, 2988) on the use of peracetic and pertungstic acids for the hydroxylation of unsaturated compounds. No experiments were described on conjugated dienes, and *cyclo*pentadiene was therefore treated with a solution of the appropriate peracid in acetic acid under various conditions, but after deacetylation and hydrogenation the resulting products contained 19—46% of 1 : 2-diol; furthermore, the 1 : 3-diol obtained was a mixture of stereoisomers. The method was therefore not of value for the present purpose.

The results of the various methods studied for the preparation of *cyclo*pentane-1 : 3-diol are summarised in Table 1.

In Table 2 the melting-points of the chief derivatives of the *cis*- and *trans*-forms of *cyclo*pentane-1 : 2- and -1 : 3-diol are given, and a consideration of these figures in the light of the evidence previously outlined makes it possible to account for most of the results of earlier investigators. The bisphenylurethane, m. p. 195°, of Dane *et al.* was clearly of the *cis*-1 : 2-diol. The two bisphenylurethanes, m. p.s 173° and 143°, of Criegee and Beucker, which were undoubtedly not 1 : 2-derivatives, were *cis*-1 : 3- and (*cis*- + *trans*-)1 : 3-compounds respectively. The derivatives prepared by Milas *et al.* (bisphenylurethane, m. p. 168—171°, and di-*p*-nitrobenzoate, m. p. 179—181°) and by Blomquist and Mayes (bisphenylurethane, m. p. 171°, and di-*p*-nitrobenzoate, m. p. 182°) were probably slightly

TABLE 1.

Source	Reagent	Overall yield of *cyclo*pentanediol, % (1 : 2 + 1 : 3)	Proportion of 1 : 2-diol in product, %
*cyclo*Pentene	SeO_2–Ac_2O	11	64
*cyclo*Pentadiene	$PhI(OAc)_2$–AcOH	19 *	49 *
,,	H_2O_2–Bu^tOH–OsO_4	19	53
,,	$Me{\cdot}CO_3H$	9–28	19—46
,,	$Me{\cdot}CO_3H$–WO_3	10—17	*ca.* 40
cis-3 : 5-Dibromo*cyclo*pentene	AgOAc–AcOH (wet)	59	81
,,	KOAc–AcOH–Ac_2O	30	63
,,	NEt_4OAc–Me_2CO	48	0
trans-3 : 5-Dibromo*cyclo*pentene	AgOAc–AcOH (wet)	19	93
,,	AgOAc–AcOH (dry)	48	42
,,	KOAc–Ac_2O	56	26
,,	NEt_4OAc–Me_2CO	46	0

* Criegee and Beucker, *loc. cit.*

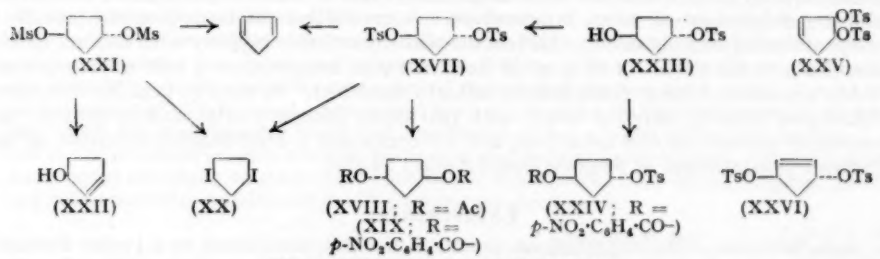
TABLE 2. *Melting points of derivatives of the* cyclo*pentane*-1 : 2- and -1 : 3-*diols.*

	cis-1 : 2	*trans*-1 : 2	*cis*-1 : 3	*trans*-1 : 3
Bisphenylurethane	197°	221°	173° *	163° *
Di-*p*-nitrobenzoate	117	143	186 *	153 *
Ditoluene-*p*-sulphonate	92	109	93	115—116
Dimethanesulphonate	82	82	92—94	89—90

* Crystallisation of a mixture of 1 : 3-stereoisomers gives a (*cis*- + *trans*-)1 : 3-bisphenylurethane, m. p. 142—144°; similarly a (*cis*- + *trans*-)1 : 3-di-*p*-nitrobenzoate has m. p. 135—140°. These mixtures are not readily separable by further recrystallisation.

impure *cis*-1 : 3-compounds, although derived from diol mixtures in each case. No explanation can be offered for the so-called *trans*-1 : 3-derivatives of Blomquist and Mayes (bisphenylurethane, m. p. 184°; di-*p*-nitrobenzoate, m. p. 207°).

Experiments on the replacement and elimination reactions of the toluene-*p*-sulphonates of the 1 : 3-diol were carried out on lines similar to those recorded in earlier papers in this



(Ms = $Me{\cdot}SO_2$–; Ts = p-$C_6H_4Me{\cdot}SO_2$–)

series. The *trans*-ditoluene-*p*-sulphonate (XVII) with potassium acetate in boiling ethanol gave some *cyclo*pentadiene together with a liquid diacetate, which was shown to have the *trans*-structure (XVIII) by deacetylation, and characterisation of the resulting

trans-1 : 3-diol by reconversion into (XVII). Similarly, (XVII) with potassium *p*-nitrobenzoate in boiling ethanol gave *cyclo*pentadiene and the *trans*-1 : 3-di-*p*-nitrobenzoate (XIX). The *cis*-ditoluene-*p*-sulphonate on similar treatment gave *cyclo*pentadiene and *cis*-1 : 3-di-*p*-nitrobenzoate. The overall retention of configuration in these experiments shows that each toluene-*p*-sulphonate group, in the *cis*- and the *trans*-series, probably undergoes normal and independent S_N2 replacement with inversion.

Replacement of the toluene-*p*-sulphonyloxy-groups in (XVII) by iodine occurred readily on treatment with sodium iodide in boiling acetone; the reaction was complete in 2 hours and gave a 62% yield of distilled 1 : 3-di-iodo*cyclo*pentane (XX). The *trans*-dimethane sulphonate (XXI) also gave (XX), but in poorer yield. Reaction of (XVII) with lithium chloride in boiling ethanol was rapid; elimination, solvolysis, and replacement by halogen all occurred, to give *cyclo*pentadiene and a liquid mixture of halide and ether. With boiling methanolic potassium hydroxide, (XVII) gave *cyclo*pentadiene and an unsaturated product, which, although it could not be purified, was probably a methoxy*cyclo*pentene. The solubility of (XVII) in aqueous alkali was too low for hydrolysis to occur, but the *trans*-dimethanesulphonate (XXI) reacted smoothly with boiling 14% aqueous potassium hydroxide to give *cyclo*pentadiene and *cyclo*pent-2-en-1-ol (XXII).

These reactions of the 1 : 3-ditoluene-*p*-sulphonates took place much more readily than those of the 1 : 2-analogues (preceding paper), probably because the deactivating effect of vicinal toluene-*p*-sulphonyloxy-groups on one another does not arise. The reactivity, however, was also noticeably greater than with the ditoluene-*p*-sulphonates of *cyclo*hexane-1 : 3-diol (Clarke and Owen, *J.*, 1950, 2103), which provides further evidence that in substitution reactions *cyclo*pentane derivatives are more reactive than their *cyclo*hexane analogues (cf. Brown, Fletcher, and Johannesen, *J. Amer. Chem. Soc.*, 1951, **73**, 212; Brown and Borkowski, *ibid.*, 1952, **74**, 1894). It is also noteworthy that the proportion of substitution to elimination was generally higher with the ditoluene-*p*-sulphonates of *cyclo*pentane-1 : 3-diol than for any other alicyclic toluene-*p*-sulphonates yet investigated.

The monotoluene-*p*-sulphonate (XXIII) of *trans-cyclo*pentane-1 : 3-diol was prepared by treatment of a pyridine solution of the *trans*-diol with 1 mol. of toluene-*p*-sulphonyl chloride in chloroform, added over a period of 3 days at 0°. It was an oil, but it was characterised by conversion into a crystalline *trans*-1-*p*-nitrobenzoate 3-toluene-*p*-sulphonate (XXIV) and also into (XVII). In striking contrast to the monotoluene-*p*-sulphonates of *cyclo*pentane-1 : 2-diol (preceding paper), it reacted only slowly with cold 0·1N-methanolic potassium hydroxide, and after 4 days at 20° only 35% reaction had occurred; in the 1 : 2-series, even the *cis*-monotoluene-*p*-sulphonate under the same conditions required only an hour for a similar degree of change, whilst the *trans*-analogue reacted exceedingly rapidly. Nevertheless, the reactivity of (XXIII), although low, was greater than that of the monotoluene-*p*-sulphonate of *trans-cyclo*hexane-1 : 3-diol, which in a comparative experiment reacted to the extent of only 10% in 4 days at 20°.

In view of the high reactivity of the halogen atoms in 3 : 5-dibromo*cyclo*pentene towards substitution by acetate ions, the *trans*-dibromide (VIII) in benzene was treated with silver toluene-*p*-sulphonate at room temperature. A crystalline ditoluene-*p*-sulphonate of a *cyclo*pentenediol was obtained; this reacted with remarkable rapidity with sodium iodide in acetone, to the extent of 60% in an hour at room temperature, a rate unprecedented for any secondary toluene-*p*-sulphonate hitherto described. Of the two possible structures (XXV) and (XXVI), only the latter, with two allylic toluene-*p*-sulphonyloxy-groups, can reasonably account for this behaviour, and the compound is accordingly formulated as the ditoluene-*p*-sulphonate of *trans-cyclo*pent-2-ene-1 : 4-diol.

Experimental

cyclo*Pentadiene*.—Di*cyclo*pentadiene, contained in a flask surmounted by a Fenske fractionating column, was heated by an oil-bath at 180° so that only the monomer distilled over. The *cyclo*pentadiene was collected in a receiver at 0°, and was dried (Na_2SO_4) and distilled (b. p. 42°) just before use.

3 : 5-*Dibromo*cyclo*pentene*.—Bromine (160 g.) in chloroform (100 c.c.) was added to a stirred solution of *cyclo*pentadiene (65 g.) in chloroform (100 c.c.) at −25° to −30°. The solvent was

immediately distilled off under reduced pressure, and the green residue was quickly distilled, to give the *cis*-dibromide (182 g., 82%), b. p. 60—63°/0·5 mm., n_D^{18} 1·5855, as a colourless liquid. The *trans*-isomer was obtained by storage of this product at room temperature in the dark, under nitrogen, for 3 months (cf. Blomquist and Mayes, *loc. cit.*). When cooled to 0°, the dark liquid then deposited the solid *trans*-compound, which was collected just before use, and washed with light petroleum (b. p. 40—60°); it formed large colourless crystals, m. p. 45°.

Tetraethylammonium Acetate.—This was prepared as the monohydrate (crystallised from acetone at −80°) by Steigmann and Hammett's method (*loc. cit.*). Crystallisation of a product containing some residual water gave material, soluble in hot acetone but only sparingly in cold, which remained solid at room temperature and was a higher hydrate. When dried over phosphoric oxide it liquefied (Found: loss, 20·3%. Calc. for $NEt_4 \cdot OAc, 4H_2O \longrightarrow NEt_4 \cdot OAc, H_2O$: loss, 20·7%), but on exposure to moist air it again crystallised.

Estimation of 1 : 2-*Diols.*—The saturated diol mixture (*ca.* 0·05 g.) was dissolved in 0·25M-sodium metaperiodate (5 c.c.) and made up to 25 c.c. with water. A similar solution, but containing no diol, was also prepared. At intervals, a 5-c.c. portion of solution was withdrawn, mixed with 10 c.c. of borax–boric acid buffer at pH 7·0 and an excess of potassium iodide, and titrated with aqueous sodium thiosulphate. In all cases the periodate consumed became constant within 24 hours. The method was checked with authentic specimens of *trans-cyclo*hexane-1 : 2-diol, and *cis*- and *trans-cyclo*pentane-1 : 2-diol.

Oxidation of cyclo*Pentene with Selenium Dioxide.*—*cyclo*Pentene (50 g.), selenium dioxide (80 g.), and acetic anhydride (144 g.) were warmed until the reaction set in; the heat produced was sufficient to maintain gentle refluxing, and selenium was deposited. The dark red reaction mixture was then heated at 100° for 6 hours, cooled, filtered from selenium, and concentrated. The residue on distillation gave a pale yellow liquid (25 g., 18%), b. p. *ca.* 113°/12 mm., which was redistilled, to give a diacetoxy*cyclo*pentene, b. p. 119—121°/13 mm., n_D^{17} 1·4620.

A portion of this product (2 g.) in ethanol (25 c.c.) was hydrogenated at atmospheric pressure in the presence of Raney nickel (only 0·64 mol. of hydrogen was absorbed) and gave a diacetoxy-*cyclo*pentane (1·5 g.), b. p. 104°/14 mm., n_D^{17} 1·4480, which was dissolved in dry methanol (5 c.c.), containing a trace of sodium, and set aside for 16 hours. After neutralisation with carbon dioxide, the solution was concentrated and distilled to give a *cyclo*pentanediol (0·7 g.), b. p. 65—70°/1·5 mm., n_D^{21} 1·4780 (Found: 1 : 2-diol, 63·8%).

Hydroxylation of cyclo*Pentadiene.*—(i) *cyclo*Pentadiene (55 g.) was added to an anhydrous solution of hydrogen peroxide in *tert.*-butanol (0·055 g./c.c.; 520 c.c.) containing a 0·5% solution of osmic acid in anhydrous *tert.*-butanol (5 c.c.), at 0°. The solution was left at 0° for 3 days and worked up as described by Milas and Maloney (*loc. cit.*). The product was distilled to give a *cyclo*pentenediol (22 g., 26%), b. p. 118°/0·5 mm., n_D^{17} 1·5040.

Hydrogenation of the *cyclo*pentenediol in ethanol in the presence of Raney nickel gave a *cyclo*pentanediol, b. p. 69—73°/0·1 mm., n_D^{19} 1·4788 (Found: 1 : 2-diol, 52·6%).

(ii) A solution containing " pertungstic acid " (cf. Mugdan and Young, *loc. cit.*) was prepared by heating a mixture of 30% aqueous hydrogen peroxide (14·5 c.c.) and acetic acid (45 c.c.) to 80° for an hour and then adding tungsten trioxide (0·2 g.; freshly precipitated from alkaline solution by acid). The peracid solution was transferred to a pressure bottle, which also contained a test tube of *cyclo*pentadiene (6·6 g.). The bottle was closed, and the reactants mixed to give a homogeneous solution. Much heat was evolved, and after the initial reaction had subsided the bottle was kept at the appropriate temperature for the required time. When cold, the dark brown solution was made alkaline with 30% aqueous sodium hydroxide, and any acetylated material was hydrolysed by heating at 100° for an hour. The hydroxylated product was isolated by continuous ether-extraction of the alkaline solution for 2 days. The ethereal extract was dried (Na_2SO_4) and concentrated to an oil, which on distillation gave a *cyclo*pentenediol. This was hydrogenated in ethanol over Raney nickel, as described above, and the 1 : 2-diol in the saturated product was then estimated with sodium metaperiodate. Hydroxylations were carried out also with the peracetic solution in the absence of any added tungsten trioxide, and with anhydrous peracetic acid. The results are given below.

Peracid	Temp.	Time, hr.	Yield, %	Unsaturated diol B. p.	Unsaturated diol n	1 : 2-Diol (%) in saturated diol
Pertungstic	60°	20	13	80—85°/0·2 mm.	1·5036/21°	40·7
,, ...	60	16	17	83—84°/0·1 mm.	1·5033/18°	39
Peracetic	60	20	28	80—85°/0·1 mm.	1·5055/14°	19
,, ...	70	96	13	82—84°/0·2 mm.	1·4982/21°	39
,, (anhyd.)	70	3	10	80—87°/0·3 mm.	1·5026/25°	46·5

Erroneous values were obtained when attempts were made to determine the 1 : 2-diol content directly on the *cyclo*pentenediol products with sodium metaperiodate; the figures ranged up to 200% of 1 : 2-diol, and the attack was evidently not restricted to the hydroxyl groups.

Reactions of cis-3 : 5-*Dibromo*cyclo*pentene with Acetates.*—(i) ***With potassium acetate in dry acetic acid.*** *cis*-3 : 5-Dibromo*cyclo*pentene (100 g.), freshly fused and finely ground potassium acetate (102 g.), and acetic acid (70 c.c.) containing acetic anhydride (10 c.c.) were heated at 100° for 18 hours. The dark liquid was poured into water (500 c.c.) and extracted with ether (4 × 100 c.c.). The extract was dried ($MgSO_4$) and worked up to give a diacetoxy*cyclo*pentene (43 g., 53%), b. p. 116—118°/2 mm., n_D^{20} 1·4652. The yield was the same as that recorded by Blomquist and Mayes. When the reaction was carried out using crude undistilled *cis*-dibromide, the overall yield of diacetate from *cyclo*pentadiene was increased to 63% (cf. 43% overall on the two stages, when distilled *cis*-dibromide was used).

The unsaturated diacetate (84 g.) was deacetylated by heating it under reflux for 5 hours with finely powdered barium hydroxide (310 g.) in ethanol (850 c.c.). The solution was cooled and filtered from precipitated barium salts, those remaining in solution being removed as carbonate by the passage of carbon dioxide. Evaporation and distillation gave a *cyclo*pentenediol (37 g., 81%), b. p. 103—105°/0·3 mm., n_D^{23} 1·5024.

The *cyclo*pentenediol (68 g.) was hydrogenated at room temp./20 atm. in ethanol (200 c.c.) in the presence of Raney nickel, to give a *cyclo*pentanediol (44·2 g., 70%), b. p. 115°/6 mm., n_D^{23} 1·4839 (Found : 1 : 2-diol, 62·8%). Its crude di-*p*-nitrobenzoate, prepared in pyridine, had m. p. 115—120° and was evidently a mixture; after several recrystallisations from ethanol and from ethyl acetate it gave a small quantity of the di-*p*-nitrobenzoate, m. p. 181—182°, of *cis-cyclo*pentane-1 : 3-diol (the authentic derivative is described below). The ditoluene-*p*-sulphonate of the saturated diol was an oil, which partly crystallised when kept. Several recrystallisations from methanol gave *trans-cyclo*pentane-1 : 2-diol ditoluene-*p*-sulphonate, m. p. 104—105°, not depressed on admixture with an authentic sample, m. p. 109° (Found : C, 55.7; H, 5·5; S, 15·4. Calc. for $C_{19}H_{22}O_6S_2$: C, 55·6; H, 5·4; S, 15·6%).

(ii) ***With silver acetate in moist acetic acid.*** A solution of the *cis*-dibromide (42 g.) in acetic acid (100 c.c.) was slowly added to a rapidly stirred suspension of freshly prepared silver acetate (from 100 g. of silver nitrate) in acetic acid (200 c.c.) containing small glass beads, so that the temperature did not exceed 30°. Stirring was maintained for a further 16 hours, and the silver salts were then filtered off and washed with acetic acid. Concentration of the filtrates and dilution with ether precipitated a further quantity of salts; evaporation of the filtered solution then gave an oil, which on distillation gave a diacetoxy*cyclo*pentene (24·3 g., 71%), b. p. 73—77°/0·5 mm., n_D^{27} 1·4639.

The product (24 g.) was dissolved in dry methanol (100 c.c.) containing sodium (*ca.* 50 mg.), and after 24 hours at room temperature the solution was neutralised with carbon dioxide and hydrogenated at room temperature and pressure over Raney nickel, the theoretical quantity of hydrogen being absorbed in 6 hours. Distillation of the product gave a *cyclo*pentanediol (11 g., 84%), b. p. 71—75°/0·5 mm. (Found : 1 : 2-diol, 81%). The ditoluene-*p*-sulphonate was obtained as a solid, which after one recrystallisation from methanol had m. p. 91—92°, undepressed on admixture with authentic *cis*-1 : 2-derivative of m. p. 92°, but depressed to *ca.* 80° with the *cis*-1 : 3-derivative of m. p. 93°. The product was therefore largely *cis-cyclo*pentane-1 : 2-diol.

(iii) ***With tetraethylammonium acetate in acetone.*** The *cis*-dibromide (165 g.) in pure acetone (200 c.c.) was added during an hour to a stirred solution of tetraethylammonium acetate (375 g.) in acetone (1300 c.c.) at <5°. Tetraethylammonium bromide began to separate almost from the beginning of the addition, and the solution became dark. The reaction mixture was kept at 0° for 16 hours, and the precipitated bromide was removed and washed with acetone until colourless. The filtrate and washings were concentrated under reduced pressure below 40°, diluted with water, and extracted with ether. The extracts were dried (Na_2SO_4) and evaporated to an oil, which on distillation gave 3 : 5-diacetoxy*cyclo*pentene (105 g., 78%), b. p. 90—95°/1·5 mm., 82—83°/0·5 mm., n_D^{25} 1·4575. Some diacetone alcohol, b. p. 63—64°/11 mm., n_D^{19} 1·4300, was isolated from the forerunnings of the distillation.

The unsaturated diacetate (104 g.) in ethanol (400 c.c.) was hydrogenated at room temp./5 atm. in the presence of Raney nickel, 1·03 mols. of hydrogen being absorbed. The resulting saturated *diacetate*, isolated by evaporation of the filtered solution, had b. p. 65°/0·3 mm., n_D^{17} 1·4492 (Found : C, 58·1; H, 7·4. $C_9H_{14}O_4$ requires C, 58·1; H, 7·6%). It was set aside in dry methanol (200 c.c.) containing sodium (0·5 g.) for 24 hours at room temperature. The

solution was then neutralised and worked up as before, to give a *cyclo*pentane-1 : 3-diol (30·7 g.), b. p. 92°/0·8 mm., n_D^{21} 1·4835, which solidified on storage at 0° (Found : 1 : 2-diol, nil). Deacetylation was also carried out by boiling the crude saturated diacetate under reflux with an excess of barium hydroxide in ethanol for 20 hours; this method gave an overall yield of 62% from the unsaturated diacetate.

Treatment of the diol (0·5 g.) with *p*-nitrobenzoyl chloride (2·0 g.) in dry pyridine (5 c.c.) gave a solid (2 g.), m. p. 117—135°, which was recrystallised three times from ethyl acetate to give the *di*-p-*nitrobenzoate* of *cis-cyclo*pentane-1 : 3-diol (0·5 g.) as needles, m. p. 186° (Found : C, 57·0; H, 4·05; N, 7·1. $C_{19}H_{16}O_8N_2$ requires C, 57·0; H, 4·0; N, 7·0%). The m. p. was depressed to 135—140° on admixture with the *trans*-isomer of m. p. 153°, described below.

The *bisphenylurethane* of *cis-cyclo*pentane-1 : 3-diol was prepared by heating a solution of the diol (0·5 g.) in phenyl *iso*cyanate (3 c.c.) for 5 minutes under reflux. The solid which separated on cooling had m. p. 159—164°, raised by successive recrystallisations from acetic acid, toluene, and ethanol, to 172° (Found : N, 8·4. $C_{19}H_{20}O_4N_2$ requires N, 8·4%). A mixture with the *trans*-isomer of m. p. 162—163° had m. p. 142—144°.

The diol (4 g.) and toluene-*p*-sulphonyl chloride (16 g.) in dry pyridine (40 c.c.) gave a ditoluene-*p*-sulphonate (11 g.), m. p. 75—87°, after one recrystallisation from methanol. This material was fractionally crystallised successively from methanol, ethyl acetate–light petroleum (b. p. 40—60°), and acetone, and gave a less-soluble fraction (0·5 g.) of *trans-cyclo*pentane-1 : 3-diol ditoluene-*p*-sulphonate, m. p. and mixed m. p. 114—115°; further crystallisation of the more soluble material from chloroform–ether gave the *cis*-isomer, m. p. 92—93°, identical with the authentic derivative described below.

cis-cyclo*Pentane*-1 : 3-*diol*.—The above di-*p*-nitrobenzoate, m. p. 186° (5 g.), was heated in dry methanol (45 c.c.) containing sodium (*ca.* 20 mg.) under reflux for an hour. The cooled solution was filtered from methyl *p*-nitrobenzoate, concentrated to 10 c.c., and diluted with water (10 c.c.); a further small amount of the methyl ester was precipitated and removed. The solution was then carefully acidified with aqueous hydrochloric acid, filtered from a little *p*-nitrobenzoic acid, and evaporated under reduced pressure. The residue was extracted with boiling chloroform, and the extracts were dried (Na_2SO_4) and evaporated to an oil, which on distillation gave cis-cyclo*pentane*-1 : 3-*diol* (0·84 g., 67%) as a very hygroscopic solid, m. p. 30—32°, b. p. 90°/1 mm. (Found : C, 58·8; H, 9·9. $C_5H_{10}O_2$ requires C, 58·8; H, 9·9%). This regenerated the original di-*p*-nitrobenzoate, m. p. 186° (from chloroform). Reaction of the diol with boiling phenyl *iso*cyanate gave the bisphenylurethane, which after recrystallisation from acetic acid–light petroleum (b. p. 40—60°) was identical (m. p. and mixed m. p. 173°) with that previously isolated from the impure *cis*-diol. The *dimethanesulphonate* was prepared by treatment of the *cis*-1 : 3-diol (0·15 g.) with methanesulphonyl chloride (0·37 g.) in pyridine (1 c.c.) at 0° for 24 hours, and precipitation by the addition of crushed ice. It crystallised from methanol in small plates, m. p. 92—94° (Found : C, 32·4; H, 5·5; S, 24.6. $C_7H_{14}O_6S_2$ requires C, 32·6; H, 5·5; S, 24·8%), depressed to 80—83° on admixture with the *trans*-isomer of m. p. 89—90°. The *ditoluene*-p-*sulphonate*, similarly obtained, crystallised from methanol in plates, m. p. 93° (Found : C, 55·7; H, 5·5; S, 15·4. $C_{19}H_{22}O_6S_2$ requires C, 55·6; H, 5·4; S, 15·6%), depressed to 80—85° on admixture with the *trans*-isomer of m. p. 114—115°.

Reactions of trans-3 : 5-*Dibromo*cyclo*pentene with Acetates*.—(i) *With silver acetate in moist acetic acid*. A suspension of freshly prepared silver acetate (from silver nitrate, 100 g.) in acetic acid (200 c.c.), containing small glass beads, was rapidly stirred during the addition of a solution of *trans*-3 : 5-dibromo*cyclo*pentene (42 g.) in acetic acid (50 c.c.); the temperature rose to 30°. Stirring was continued for 16 hours, and the product was then isolated as described for the corresponding reaction with the *cis*-dibromide; distillation gave a diacetoxy*cyclo*pentene (19·2 g., 56%), b. p. 68—70°/0·2 mm., n_D^{16} 1·4677, which was hydrolysed by being boiled under reflux with barium hydroxide (73 g.) in ethanol (200 c.c.) for 5 hours. The solution was cooled and filtered, and barium salts remaining in solution were precipitated as carbonate by passage of carbon dioxide. Filtration, evaporation, and distillation of the residual oil gave a *cyclo*pentenediol (5·1 g., 48%), b. p. 83—84°/0·5 mm., n_D^{18} 1·4957. This was dissolved in ethanol (30 c.c.) and hydrogenated at room temperature and pressure over Raney nickel; 0·97 mol. of hydrogen was absorbed. The catalyst was removed and the filtrate worked up to give a *cyclo*pentanediol (3·4 g., 68%), b. p. 60—66°/0·1 mm., which crystallised to a very hygroscopic solid (Found : 1 : 2-diol, 93%).

The diol (0·91 g.) with *p*-nitrobenzoyl chloride (3·55 g.) in pyridine (20 c.c.) gave a solid (4·1 g.), which after recrystallisation from ethanol gave *cis-cyclo*pentane-1 : 2-diol di-*p*-nitrobenzoate, m. p. and mixed m. p. 117°. The product was therefore almost pure *cis*-1 : 2-diol.

(ii) *With silver acetate in dry acetic acid.* The quantities used were identical with those in the preceding description, but the silver acetate was dried over phosphoric oxide under reduced pressure and the acetic acid was dehydrated by distillation from an excess of acetic anhydride. The unsaturated diacetate (27·8 g., 80%), b. p. 75—79°/0·5 mm., n_D^{31} 1·4510, was deacetylated by treatment with a catalytic amount of sodium in methanol and then hydrogenated as above, to give a *cyclo*pentanediol (9 g.), b. p. 80—81°/0·8 mm. (Found: 1 : 2-diol, 42%).

A portion (1 g.) of the diol was treated with toluene-*p*-sulphonyl chloride (5 g.) in pyridine (10 c.c.) at 0° for 24 hours. Addition of crushed ice precipitated an oil. A solution of this in chloroform was washed successively with water, dilute hydrochloric acid, and sodium hydrogen carbonate solution, dried ($CaCl_2$), and evaporated to a semi-solid residue, which furnished a solid, m. p. 90—95°, when recrystallised once from methanol (10 c.c.). Fractional crystallisation of this solid from chloroform–ether gave a less-soluble fraction (0·3 g.) of *trans-cyclo*pentane-1 : 2-diol ditoluene-*p*-sulphonate, m. p. and mixed m. p. 109°. Further crystallisations (from the same solvent) of the more soluble material gave *cis-cyclo*pentane-1 : 3-diol ditoluene-*p*-sulphonate, m. p. and mixed m. p. 91—92° (depressed to 70—75° by the *cis*-1 : 2-isomer). Evaporation of the original methanolic mother-liquors left a sticky solid which after 3 recrystallisations from chloroform–ether gave the *trans*-1 : 3-ester, m. p. and mixed m. p. 114°.

(iii) *With potassium acetate in acetic anhydride.* A mixture of the *trans*-dibromide (38 g.), anhydrous potassium acetate (60 g.), and acetic anhydride (200 c.c.) was heated gradually to the b. p.; a vigorous reaction occurred and the liquid continued to boil without further application of heat. When cold the dark brown mixture was cautiously diluted with water and extracted with ether. Evaporation of the dried (Na_2SO_4) extracts gave an oil which on distillation furnished a diacetoxy*cyclo*pentene (27·7 g., 89%), b. p. 90°/0·4 mm., n_D^{21} 1·4572. This was deacetylated by treatment in the usual way with dry methanol containing a small quantity of sodium, and then hydrogenated in the same solution (after neutralisation) over Raney nickel at room temperature and pressure to give a *cyclo*pentanediol (9·6 g.), b. p. 82°/0·3 mm. (Found: 1 : 2-diol, 26%).

The ditoluene-*p*-sulphonate, prepared from the diol (1 g.) as described above, on fractional crystallisation from methanol, followed by chloroform–ether, gave *trans-cyclo*pentane-1 : 3-diol ditoluene-*p*-sulphonate (0·3 g.), m. p. and mixed m. p. 114°.

(iv) *With tetraethylammonium acetate in acetone.* The *trans*-dibromide (50 g.) in acetone (100 c.c.) was added to a stirred solution of tetraethylammomium acetate (120 g.) in acetone (500 c.c.), cooled in an ice-bath, at such a rate that the temperature did not rise above 5°. Tetraethylammonium bromide began to separate immediately, and the solution became dark. After the addition was complete (1 hour), the mixture was kept at 0° for 16 hours and then filtered from tetraethylammonium bromide (90 g., 97%). The solid was washed with acetone until colourless, and the combined filtrate and washings were concentrated under reduced pressure and diluted with water (400 c.c.). The aqueous mixture was extracted with ether (3 × 100 c.c.) and the dried (Na_2SO_4) extracts were evaporated to a dark liquid, which on distillation gave *trans*-3 : 5-diacetoxy*cyclo*pentene (28·8 g., 70%), b. p. 75—76°/0·5 mm., n_D^{19} 1·4635, as a pale yellow liquid. Two further preparations gave yields of 73 and 83%.

The unsaturated diacetate (28·5 g.) was hydrogenated in ethanol (100 c.c.) at room temperature and atmospheric pressure in the presence of Raney nickel; 0·97 mol. of hydrogen was absorbed. The saturated diacetate was not isolated; the filtered ethanolic solution was directly hydrolysed under reflux with barium hydroxide (110 g.) for 5 hours. The barium salts were filtered off, and after removal of dissolved salts by passage of carbon dioxide, and further filtration, the solution was concentrated under reduced pressure to a viscous liquid which on distillation gave trans-cyclo*pentane*-1 : 3-*diol* (8·73 g., 55%), b. p. 80—85°/0·1 mm., as a colourless liquid, with a pleasant odour, which solidified to a crystalline, very hygroscopic solid, m. p. 40° (Found: 1 : 2-diol, nil; C, 58·8; H, 9·9. $C_5H_{10}O_2$ requires C, 58·8; H, 9·9%).

In further preparations, the saturated diacetate was isolated as an oil (by evaporation of the filtered hydrogenation product) and was deacetylated by treatment with dry methanol containing a catalytic amount of sodium. The yield of *trans*-1 : 3-diol was approximately the same as that obtained by hydrolysis with barium hydroxide.

Derivatives of trans-cyclo*Pentane*-1 : 3-*diol*.—Treatment of the diol (0·24 g.) with *p*-nitrobenzoyl chloride (0·96 g.) in pyridine (3 c.c.) for 24 hours at 0° gave, on precipitation in ice-water, a solid (0·9 g.), m. p. 140—148°, which after two recrystallisations from ethyl acetate gave needles of the trans-*di*-p-*nitrobenzoate*, m. p. 153° (Found: C, 56·9; H, 4·4; N, 7·3. $C_{19}H_{16}O_8N_2$ requires C, 57·0; H, 4·0; N, 7·0%).

The *trans*-1 : 3-diol (0·5 g.) was heated under reflux with phenyl *iso*cyanate (3 c.c.) for 5

minutes. On cooling, a solid separated, m. p. 145—155°, which was crystallised twice from acetic acid–light petroleum (b. p. 40—60°) to give fine needles of the trans-*bisphenylurethane*, m. p. 162—163 (Found: N, 8·7; $C_{19}H_{20}O_4N_2$ requires N, 8·4%).

A solution of methanesulphonyl chloride (6·0 g.) in pyridine (20 c.c.) was added slowly to a stirred solution of *cyclo*pentane-1 : 3-diol (2·4 g.) in pyridine (10 c.c.) cooled to −10°. The mixture was stored at 0° for 16 hours, and crushed ice was then added. The precipitated trans-*dimethanesulphonate* crystallised from methanol in needles, m. p. 89—90° (Found: C, 32·7; H, 5·7; S, 24·8. $C_7H_{14}O_6S_2$ requires C, 32·6; H, 5·5; S, 24·8%).

Similar treatment of the *trans*-1 : 3-diol (0·43 g.) in pyridine (2 c.c.) with toluene-*p*-sulphonyl chloride (1·72 g.) in pyridine (5 c.c.) followed by storage for 16 hours at 0° gave the trans-*ditoluene*-p-*sulphonate*, small nodules (from methanol), m. p. 114—115° (Found: C, 55·7; H, 5·5; S, 15·4. $C_{19}H_{22}O_6S_2$ requires C, 55·6; H, 5·4; S, 15·6%).

Reactions of the Ditoluene-p-*sulphonate of* trans-cyclo*Pentane*-1 : 3-*diol*.—(i) *With potassium acetate*. The ditoluene-*p*-sulphonate (3 g.) and fused potassium acetate (3·5 g.) were heated in dry ethanol (60 c.c.) under reflux, a slow current of nitrogen being passed through the apparatus and then through a wash-bottle containing a 1% solution of sodium nitroprusside in 1% methanolic potassium hydroxide. The latter became red in a few minutes, indicating the formation of *cyclo*pentadiene (Scagliarina and Lucchi, *Chem. Abs.*, 1940, **34**, 2287), and potassium toluene-*p*-sulphonate began to be precipitated from the reaction mixture. Boiling was maintained for 12 hours, and the salt was then removed by filtration (2·75 g., 90%). The filtrate was evaporated under reduced pressure and the residue was dissolved in water (50 c.c.) and extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated to an oil, which on distillation gave the diacetate of *trans-cyclo*pentane-1 : 3-diol as a colourless mobile liquid (0·54 g., 43%), b. p. 65—68°/0·5 mm., n_D^{20} 1·4454.

The diacetate was deacetylated by treatment in dry methanol with a catalytic amount of sodium, and worked up as previously described, to give the *trans*-1 : 3-diol (0·24 g.), which was characterised by treatment with toluene-*p*-sulphonyl chloride (0·95 g.) in dry pyridine (3 c.c.) at 0° to give the *trans*-ditoluene-*p*-sulphonate, m. p. and mixed m. p. 114—115°.

(ii) *With potassium* p-*nitrobenzoate*. The ditoluene-*p*-sulphonate (1 g.) and potassium *p*-nitrobenzoate (2·5 g.) in dry ethanol (75 c.c.) were heated under reflux in a current of nitrogen for 8 hours; *cyclo*pentadiene was detected as in the previous experiment. The reaction mixture was cooled, diluted with water (30 c.c.), and distilled under reduced pressure to remove most of the alcohol. The residual solution was extracted with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave a solid residue, which on recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°) gave the *trans-cyclo*pentane-1 : 3-diol di-*p*-nitrobenzoate, m. p. and mixed m. p. 153°.

(iii) *With sodium iodide*. A solution of the ditoluene-*p*-sulphonate (1·5 g.) and sodium iodide (2·5 g.) in dry acetone (30 c.c.) was boiled under reflux for 2 hours in a slow stream of nitrogen, *cyclo*pentadiene being detected in the issuing gases as previously described. The precipitated sodium toluene-*p*-sulphonate was filtered off (1·38 g., 98%), and the solution was evaporated to a semi-solid residue. This was diluted with water, and the oil which separated was extracted with ether. The extracts were washed with aqueous sodium thiosulphate solution, dried (Na_2SO_4), and concentrated to an oil, which on distillation gave trans-1 : 3-*di-iodo*cyclo*pentane* (0·73 g., 62%), b. p. 55—60°/0·0005 mm., n_D^{19} 1·6490 (Found: I, 77·2. $C_5H_8I_2$ requires I, 78·8%), as a pale yellow liquid which did not wet glass.

(iv) *With lithium chloride*. The ditoluene-*p*-sulphonate (1·65 g.) and anhydrous lithium chloride (0·7 g.) were heated under reflux in ethanol (30 c.c.) under reflux in a current of nitrogen. After 6 hours no more *cyclo*pentadiene could be detected in the gas, and the solution, which was now acid, was neutralised with aqueous sodium hydroxide and concentrated to small volume. Extraction with ether gave a colourless liquid (0·14 g.), b. p. 58°/28 mm., n_D^{15} 1·4618, which showed no unsaturation towards bromine in carbon tetrachloride, and was probably a mixture of chloro- and ethoxy-compounds (Found: C, 54·4; H, 8·5; Cl, 29·0. Calc. for $C_5H_8Cl_2$: C, 43·2; H, 5·8; Cl, 51·0. Calc. for $C_9H_{18}O_2$: C, 68·3; H, 11·5%).

(v) *With methanolic potassium hydroxide*. A solution of the ditoluene-*p*-sulphonate (3 g.) in 5% methanolic potassium hydroxide (40 c.c.) was boiled under reflux in a current of nitrogen. A considerable quantity of *cyclo*pentadiene was formed, as judged from the rapid formation of a red precipitate in the nitroprusside trap, and after 1 hour the reaction was over. Potassium toluene-*p*-sulphonate (2 g.) was filtered from the cooled solution, and the filtrate was concentrated to small volume (1 atm.; Fenske column). The residue was diluted with water and extracted with pentane, but gave no product. The methanolic distillate was strongly un-

saturated to bromine in carbon tetrachloride and to neutral aqueous potassium permanganate, but gave a negative reaction for *cyclo*pentadiene; it probably contained a methoxy*cyclo*pentene, since treatment with a slight excess of bromine and evaporation gave a colourless saturated oil (0·2 g.), b. p. 100°/20 mm., n_D^{20} 1·4972 (Found: C, 35·9; H, 5·5; Br, 47·7. Calc. for a bromodimethoxy*cyclo*pentane, $C_7H_{13}O_2Br$: C, 40·2; H, 6·3; Br, 38·3. Calc. for a dibromomethoxy*cyclo*pentane, $C_6H_{10}OBr_2$: C, 27·9; H, 3·9; Br, 62·0%).

Reactions of the Dimethanesulphonate of trans-cyclo*Pentane*-1 : 3-*diol*.—(i) *With sodium iodide*. The dimethanesulphonate (1·25 g.) and sodium iodide (3·1 g.) were boiled under reflux in acetone (35 c.c.), in a slow stream of nitrogen. The formation of *cyclo*pentadiene was detected as described above, and sodium methanesulphonate began to be precipitated within a few minutes. After 3 hours the solution was cooled, filtered, and worked up as for the similar reaction with the ditoluene-*p*-sulphonate, to give 1 : 3-di-iodo*cyclo*pentane (0·55 g., 35%), b. p. 65°/0·001 mm., n_D^{23} 1·6345, which was much darker than the product previously obtained.

(ii) *With aqueous potassium hydroxide*. A suspension of the dimethanesulphonate (4·7 g.) in a solution of potassium hydroxide (4·7 g.) in water (30 c.c.) was boiled under reflux in a current of nitrogen. After 1½ hours, when no more *cyclo*pentadiene was being evolved, the solution was steam-distilled. The distillate was continuously extracted with ether overnight; evaporation of the dried (Na_2SO_4) extracts gave an unsaturated oil which was distilled, to give *cyclo*pent-2-enol (0·71 g., 46%), b. p. 138—140°, n_D^{20} 1·4735, characterised as the phenylurethane, m. p. 127° (Dane *et al.*, *loc. cit.*, give m. p. 128—129°). The residue from the steam-distillation was neutralised with hydrochloric acid and continuously extracted with ether, to give a very small amount of oil (0·01 g.), identified as *trans-cyclo*pentane-1 : 3-diol by conversion into the di-*p*-nitrobenzoate; the amount available was insufficient for the m. p. to be raised above 147—150°, but a mixed m. p. with the authentic *trans*-derivative (m. p. 153°) was 150—153°.

Reaction of the Ditoluene-p-*sulphonate of* cis-cyclo*Pentane*-1 : 3-*diol with Potassium* p-*Nitrobenzoate*.—The ditoluene-*p*-sulphonate (1·05 g.) and potassium *p*-nitrobenzoate (2·5 g.) were boiled under reflux in dry ethanol (75 c.c.) for 8 hours under nitrogen; *cyclo*pentadiene was evolved and detected as previously described. The reaction mixture was worked up as for the similar reaction with the *trans*-ditoluene-*p*-sulphonate and gave a solid (0·15 g.), m. p. 175—182°, which after one recrystallisation from chloroform furnished the di-*p*-nitrobenzoate of *cis-cyclo*pentane-1 : 3-diol, m. p. and mixed m. p. 186°.

Monotoluene-p-*sulphonate of* trans-cyclo*Pentane*-1 : 3-diol.—A solution of toluene-*p*-sulphonyl chloride (9·8 g.) in chloroform (100 c.c.) was added in small portions, during 3 days, to a stirred solution of the *trans*-1 : 3-diol (5·0 g.) in dry pyridine (100 c.c.) at <0°. The mixture was stored for a further day at 0° and then concentrated under reduced pressure. The residue was diluted with water (250 c.c.), and the precipitated oil was taken up in chloroform and washed successively with dilute sulphuric acid, water, and aqueous sodium hydrogen carbonate; evaporation of the dried (Na_2SO_4) solution, finally at 0·0001 mm., gave the *monotoluene*-p-*sulphonate* (5·4 g., 43%) as a pale yellow viscous oil, n_D^{14} 1·5338 (Found: S, 12·7. $C_{12}H_{16}O_4S$ requires S, 12·5%). It was characterised by conversion of portions in pyridine into the *trans*-ditoluene-*p*-sulphonate, m. p. and mixed m. p. 114—115°, and the p-*nitrobenzoate toluene*-p-*sulphonate* of *trans-cyclo*pentane-1 : 3-diol, which after recrystallisation from methanol had m. p. 82—83° (Found: C, 56·3; H, 4·8; N, 3·3. $C_{19}H_{19}O_7NS$ requires C, 56·3; H, 4·7; N, 3·5%).

Rates of Reaction with Methanolic Potassium Hydroxide of the Monotoluene-p-*sulphonates of* trans-cyclo*Pentane- and* trans-cyclo*Hexane*-1 : 3-*diol*.—Solutions of the *cyclo*pentane compound (1·874 g.) in 0·0746N-methanolic potassium hydroxide (200 c.c.), and the *cyclo*hexane compound (prepared by the method of Clarke and Owen, *loc. cit.*) (1·992 g.) in 0·0748N-methanolic potassium hydroxide (200 c.c.) were kept at 20°, portions being withdrawn from time to time and titrated with standard aqueous sulphuric acid (phenolphthalein). The results are shown below:

Time, hr.		26	48	72	96
Reaction (%)	*cyclo*pentane deriv. ...	11	17	24	34
	*cyclo*hexane deriv.	2	—	—	10

Ditoluene-p-*sulphonate of* trans-cyclo*Pent*-2-*ene*-1 : 4-*diol*.—A solution of *trans*-3 : 5-dibromo-*cyclo*pentene (5 g.) in dry benzene (25 c.c.) was slowly added to a stirred suspension of silver toluene-*p*-sulphonate (25 g.) in dry benzene (75 c.c.), containing glass beads. Stirring was maintained for 16 hours at room temperature, and the silver salts were then filtered off and washed with dry benzene. The solution was concentrated below 35° under reduced pressure to about 10 c.c., and then diluted with light petroleum (b. p. 40—60°) and cooled to 0°. A crystalline

solid (3·2 g.), m. p. 63—65°, was thus obtained, and a further quantity (1·9 g.) with the same m. p. was precipitated on the addition of more light petroleum (total yield, 66%). A small quantity was recrystallised from carbon tetrachloride, to give trans-cyclo*pent*-2-*ene*-1 : 4-*diol ditoluene*-p-*sulphonate*, m. p. 64—65° (Found : S, 15·2. $C_{19}H_{20}O_6S_2$ requires S, 15·7%), but an attempt to recrystallise the bulk of the material in this way resulted in gross decomposition, with formation of tar and acid.

Reaction with sodium iodide. The above ditoluene-*p*-sulphonate (0·14 g.) was added to a solution of sodium iodide (0·24 g.) in dry acetone (10 c.c.). The mixture became warm, sodium toluene-*p*-sulphonate began to be precipitated, and a brown colour developed in a few minutes. After 1 hour the salt was filtered off (0·08 g., 60%) and the free iodine (54%) was estimated by thiosulphate; *cyclo*pentadiene was detected in the solution with alkaline nitroprusside. Since the amount of free iodine almost corresponded to the quantity of sodium toluene-*p*-sulphonate formed, no appreciable amount of di-iodo*cyclo*pentene could be present.

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772. *The Synthesis of Sugars from Simpler Substances. Part III.* Enzymic Synthesis of a Pentose.*

By L. HOUGH and J. K. N. JONES.

Glycollic aldehyde and triose phosphate condense in the presence of an aldolase preparation from peas, to give D-xylulose. The metabolism of pentoses is discussed.

THE biogenesis of the pentose sugars in the plant cell is obscure. It has been postulated (Tewfik and Stumpf, *Amer. J. Bot.*, 1949, **36**, 567; Schlenk, *Adv. Enzymology*, 1949, **9**, 455; Hough and Jones, *Nature*, 1951, **167**, 180; *J.*, 1951, 1122, 3191) that they arise by the combination of a diose with a triose, in an analogous manner to fructose and sorbose which are derived by combination of two triose units in the presence of "aldolase," an enzyme present in practically all living cells. This hypothesis is supported by the observations that aldolase preparations from both animal (Meyerhof, Lohmann, and Schuster, *Biochem. Z.*, 1936, **286**, 301, 319; Dische, *Naturwiss.*, 1938, **26**, 252; Schlenk and Waldvogel, *Fed. Proc.*, 1947, **6**, 288; *Arch. Biochem. Biophys.*, 1949, **22**, 185; Racker, *Fed. Proc.*, 1948, **7**, 180; Sable, *Biochim. Biophys. Acta*, 1952, **8**, 687) and bacterial origin (Marmur and Schlenk, *Arch. Biochem. Biophys.*, 1951, **31**, 154; Racker, *Nature*, 1951, **167**, 408; Kaushal, Jowett, and Walker, *ibid.*, 1951, **167**, 949; Rappaport, Barker, and Hassid, *Arch. Biochem. Biophys.*, 1951, **31**, 326; Sable, *loc. cit.*) catalyse the reversible condensation of triose phosphate with glycollic aldehyde or acetaldehyde, to give pentose phosphate or deoxypentose phosphate respectively, although the deoxypentose(s) has not yet been identified. On the other hand, there is little evidence to relate aldolase with the biosynthesis of pentoses in the plant, and, furthermore, there appears to be a second mode of synthesis of pentose operative, which involves oxidative decarboxylation of hexonic acids (see below). A third possibility, involving enzymic decarboxylation of hexuronic acids, has been but little investigated. Tewfik and Stumpf (*loc. cit.*) have observed the occurrence in a wide variety of plants, particularly the pea, of an aldolase which appears to be similar to that isolated from animals and bacteria. The term "aldolase" usually refers to an amorphous enzyme preparation containing, amongst other materials, an enzyme capable of splitting hexose diphosphate into two triose phosphates and possibly pentose phosphate

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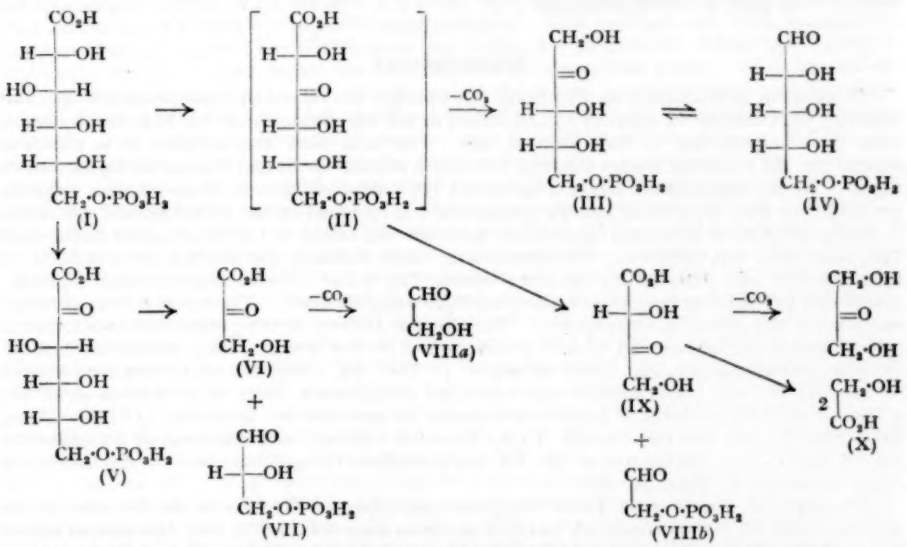
into triose and diose fragments, although it is conceivable that a separate enzyme may be responsible for splitting pentose.

We have attempted the synthesis of pentose from glycollic aldehyde and triose phosphates which were prepared by treating the sodium salt of D-fructose-1 : 6 diphosphate in the presence of sodium fluoride with an aldolase preparation extracted from peas (Stumpf, *J. Biol. Chem.*, 1948, **176**, 233). Glycollic aldehyde was introduced into the reaction mixture and the pH of the solution adjusted to 6·5. This may not be the optimum pH, but was chosen deliberately in order to avoid the possibility of the purely chemical combination of glycollic aldehyde with triose phosphate which is known to occur in the absence of enzyme in alkaline solution (Hough and Jones, *loc. cit.*). At intervals, the reaction mixture was analysed for pentose sugars by the furfuraldehyde method; pentose was rapidly produced. Examination on paper chromatograms suggested the formation of pentose phosphate, followed by dephosphorylation to free ketopentose. The aldolase preparation was observed to contain phosphatase. After 72 hours at 20°, the reaction mixture was heated to inactivate the enzymes, centrifuged, and evaporated. The residue was extracted with alcohol and the extract evaporated to a syrup, which was then subjected to partition chromatography on a column of cellulose to give a fraction containing ketopentose and a little ribose. These pentose sugars were recognised on paper chromatograms from their rates of movement in various solvent systems and from the characteristic red colour given by both with *p*-anisidine hydrochloride and the characteristic blue colour given only by the ketopentose with resorcinol–hydrochloric acid (Hough and Jones, *loc. cit.*). In a control experiment, in which glycollic aldehyde was omitted from the reaction mixture, the products contained ribose, but no ketopentose. The ribose probably arises from D-fructose 1 : 6-diphosphate by conversion into D-glucose 6-phosphate followed by oxidative decarboxylation to D-ribose (Dickens, *Biochem. J.*, 1938, **32**, 1626, 1636; Dickens and Glock, *Nature*, 1950, **166**, 33; *Biochem. J.*, 1951, **50**, 81; Scott and Cohen, *Science*, 1950, **111**, 543; *J. Biol. Chem.*, 1951, **188**, 509; Horecker, Smyrniotis, and Seegmiller, *ibid.*, 1951, **193**, 383), since fluoride inhibits neither glucose 6-phosphate dehydrogenase nor the oxygen uptake of 6-phosphogluconate. The ketopentose was separated from the ribose by sheet-paper chromatography and isolated as a syrup. It moved at the same rate as did xylulose on paper chromatograms. After epimerisation of the ketose in pyridine at 100°, a strong spot corresponding to xylose and weak spots corresponding to arabinose and ribose were detected on paper chromatograms; authentic xylulose gave the same sugars after epimerisation. The arabinose and ribose probably arise by $C_{(3)}$-racemisation, as in the formation of D-tagatose and D-sorbose from D-galactose (Lobry de Bruyn and van Eckenstein, *Rec. Trav. chim.*, 1900, **19**, 5) and the epimerisation of D-fructose to D-glucose, D-mannose, and D-allulose (Wolfrom, Lew, and Goepp, *J. Amer. Chem. Soc.*, 1946, **68**, 1443) and of D-manno-D-*gala*heptose to D-glucoheptulose and D-mannoheptulose (Montgomery and Hudson, *ibid.*, 1939, **61**, 1654). Reaction of the ketopentose with aqueous phenylhydrazine acetate afforded a crystalline pentosazone (m. p. 165—167°) which was optically active and exhibited mutarotation ($[\alpha]_D$ −16° ⟶ −43°), as did D-xylosazone (-lyxosazone). It has been noted that DL-xylosazone has m. p. 205°, approximately 40° above that of the individual D- and L-isomers, whereas that of DL-ribosazone (-arabinosazone) is only slightly (*ca.* 5°) above that of the optically active osazones, thus providing a method of identification (Fischer, *Ber.*, 1894, **27**, 2486; Levene and La Forge, *J. Biol. Chem.*, 1914, **18**, 319). We confirmed these observations and observed that the melting point of our pentosazone was elevated (m. p. 190—192°) on admixture with L-xylosazone, but not with D- or L-ribosazone or D-xylosazone. On this evidence, the osazone is identified as a derivative of D-xylulose.

A preliminary account of these results has been given elsewhere (Forrest, Hough, and Jones, *Chem. and Ind.*, 1951, 1093). It seems therefore that glycollic aldehyde and triose phosphate combine in the presence of the pea enzyme to yield D-xylulose (2-keto-D-xylitol). This is of interest because D-xylulose is a possible precursor of D-xylose, which is of wide occurrence in Nature and is present in the pea as a xylan. Pentose phosphate isomerase remains to be detected in plants, but it is noteworthy that Horecker, Smyrniotis, and Seegmiller (*loc. cit.*) have found D-ribose phosphate isomerase in yeast and in rat liver (Horecker and Smyrniotis, *J. Amer. Chem. Soc.*, 1952, **74**, 2123) and that D-ribulose phos-

phate is the precursor of D-ribose. Benson (*ibid.*, 1951, **73**, 2970) detected a D-ribulose diphosphate in the products formed during the first few seconds of $^{14}CO_2$ photosynthesis. L-Xylulose has been found in human pentosuria (Levene and La Forge, *loc. cit.*) and it would appear that bacteria metabolise D-xylose and L-arabinose by way of ketopentoses (Lampen, Gest, and Sowdon, *J. Bact.*, 1951, **61**, 97; Rappaport, Barker, and Hassid, *loc. cit.*). Reference has been made by Dische and Borenfreund (*J. Biol. Chem.*, 1951, **192**, 583) to the preparation by Dr. E. Racker of xylulose 1-phosphate from glycollic aldehyde and dihydroxyacetone phosphate in the presence of an aldolase.

Early work on pentose metabolism was largely concerned with the oxidation of D-glucose to pentose, and it has been established that D-glucose-6-phosphate is oxidised by yeast and liver preparations to 6-phospho-D-gluconate (I), followed by oxidative decarboxylation to D-ribose 5-phosphate (IV) (Dickens, *loc. cit.*; Dickens and Glock, *loc. cit.*; Cohen and Scott, *loc. cit.*; Horecker and Smyrniotis, *Arch. Biochem. Biophys.*, 1950, **29**, 232; *J. Biol. Chem.*, 1951, **193**, 371). Cohen and Scott (*loc. cit.*) also detected D-arabinose in the oxidation products, but investigations by Horecker, Smyrniotis, and Seegmiller (*loc. cit.*) suggest that arabinose 5-phosphate is not an intermediary in the conversion of 6-phospho-D-gluconic acid (I) into D-ribose 5-phosphate (IV). Since D-ribose is produced from D-gluconic acid, a stereochemical inversion must occur at $C_{(2)}$ of the pentose; simple degradation would give D-arabinose. Horecker, Smyrniotis, and Seegmiller (*loc. cit.*) found that D-ribulose 5-phosphate (III) is a precursor of D-ribose 5-phosphate (IV) and that an equilibrium mixture of the two is formed, the interconversion being catalysed by pentose phosphate isomerase. They postulate oxidation at $C_{(3)}$ in the 6-phosphogluconate with formation of 3-keto-6-phospho-D-gluconic acid (II) (a phosphorylated analogue of the open-chain form of vitamin C), which on decarboxylation could yield D-ribulose 5-phosphate (III) (cf. the oxidative degradation of fats at the β-carbon atom). 3-Keto-6-phospho-D-gluconic acid remains to be detected in this system, and it also remains to separate the oxidative step from the decarboxylation reaction.



This scheme is more feasible than that based on the intermediary formation of an enediol (Dickens and Glock, *loc. cit.*; Cohen and Scott, *loc. cit.*). Bernstein (*J. Amer. Chem. Soc.*, 1951, **73**, 5003), using ^{14}C-acetate, has observed that the direct conversion of hexose into D-ribose is not the major pathway in animal metabolism, and suggests that synthesis is achieved by the combination of two- and three-carbon units which would account for the accumulation of glyceraldehyde 3-phosphate (VII) in the experiments of

Scott and Cohen (*loc. cit.*) and also the stereochemical inversion. Alternatively, it is possible that 6-phosphogluconic acid is oxidised to 2-keto-6-phospho-D-gluconic acid (V), which then splits to give D-glyceraldehyde 3-phosphate (VII) and hydroxypyruvic acid (VI). The latter on enzymic decarboxylation yields glycollic aldehyde (VIII*a*), which on recombination with D-glyceraldehyde 3-phosphate (VII) may yield D-ribose 5-phosphate (cf. Hough and Jones, *Nature*, 1951, **167**, 180; Akabori, Uchara, and Muramatsu, *Proc. Jap. Acad.*, 1952, **28**, 39). If, on the other hand, 3-ketogluconic acid 6-phosphate (II) is produced, a split into glycollic aldehyde phosphate (VIII*b*) and dihydroxyacetoacetic acid (IX) might occur; the latter, losing carbon dioxide, would yield dihydroxyacetone and hence ketopentose 5-phosphate on combination with glycollic aldehyde phosphate (VIII*b*). Alternatively, dihydroxyacetoacetic acid (IX) could be envisaged as splitting into two molecules of glycollic acid (X).

The detection of sedoheptulose amongst the early products of photosynthesis by plants has led Benson *et al.* (*J. Amer. Chem. Soc.*, 1951, **73**, 2970; *J. Biol. Chem.*, 1952, **196**, 703) to the belief that its phosphate esters play a vital rôle in photosynthesis. Horecker and Smyrniotis (*J. Amer. Chem. Soc.*, 1952, **74**, 2123) have observed the enzymic synthesis of sedoheptulose phosphate from pentose phosphate under the combined influence of a pentose-splitting enzyme from rat liver and crystalline muscle aldolase (Taylor, Green, and Cori, *J. Biol. Chem.*, 1948, **173**, 591). Heptulose phosphate was also formed from D-erythrose and hexose 1 : 6-diphosphate in the presence of an aldolase, which suggests that synthesis from pentose phosphate is achieved by fission into triose and diose, two molecules of diose combining to yield a tetrose, a reaction known to occur *in vitro* (Fenton, *J.*, 1900, 129; Hough and Jones, *loc. cit.* and unpublished observations), and combination with dihydroxyacetone phosphate would yield heptulose phosphate.

It is becoming increasingly manifest that the ketopentose phosphates play an important part in plant and animal metabolism, because of their possible transformations into hexose, tetrose, and heptulose sugars, and their rôle as a precursor of the aldopentoses which play such a vital part in living material.

Experimental

Preparation of Aldolase from Pea Seeds (cf. Stumpf, *loc. cit.*).—Dry pea seeds (500 g.; *var.* Onward) were steeped in water (1 l.) and stored in the refrigerator at 2° for 24 hours, by which time they had swollen to their normal size. The peas were disintegrated in a top-drive macerator, the resultant sludge strained through a muslin cloth, and the turbid liquor centrifuged. To the supernatant liquor a saturated (20°) neutral solution of ammonium sulphate was added to 35% saturation, and the precipitate was removed on the centrifuge and discarded. A further portion of saturated ammonium sulphate was added to the supernatant liquid until 70% saturation was obtained. The precipitate, which contains the aldolase, was isolated on the centrifuge and dialysed for 18 hours against tap water to remove ammonium sulphate; coagulated protein was removed on the centrifuge and discarded. The solution thus obtained was used in the following experiments. The aldolase activity of the preparation was found to be 0·04 unit of aldolase per mg. of solid as determined by the cyanide-fixing method of Herbert, Gordon, Subrahmanyan, and Green (*Biochem. J.*, 1940, **34**, 1108), the unit being that defined by Stumpf (*loc. cit.*). The solution also contained phosphatase, since on incubation at 37° for 1 hour with 0·5% of sodium β-glycerophosphate as specified by Bodansky (*J. Biol. Chem.*, 1933, **101**, 33), the enzyme solution (1 c.c.) liberated 1·08 mg. of phosphorus as phosphate at pH 8·6, and 1·7 mg. phosphorus at pH 6·5, the phosphate being determined by the method of Allen (*Biochem. J.*, 1940, **34**, 858).

Formation of Pentose from Triose Phosphate and Glycollic Aldehyde in the Presence of Pea Aldolase (with R. S. Forrest).—A mixture of the enzyme solution (5 c.c.), the sodium salt of hexose diphosphate (0·25 g.) in water (5 ml.), phosphate buffer (pH 6·5; 10 c.c.), and a neutral solution (10 c.c.) of glycollic aldehyde (prepared from 0·5 g. of dihydroxymaleic acid by decarboxylation) was covered with a layer of toluene and incubated at 30°. At intervals, portions of the reaction mixture were removed and the pentose concentration was determined by Youngburg and Pacher's method (*J. Biol. Chem.*, 1927, **73**, 599). This method is a colorimetric procedure depending on the production of colour from furfuraldehyde and aniline acetate; xylose was used for the construction of the calibration curve. The pentose concentration increased until

after 20 hours, when the yield (calculated as xylose) corresponded to 3·6% as derived from dihydroxymaleic acid.

Isolation of Ketopentose.—A mixture of the enzyme solution (100 c.c.), a solution (25 c.c.) of the sodium salt of hexose diphosphate (7·37 g.), glycollic aldehyde solution (200 c.c. prepared by decarboxylation of 10·7 g. of dihydroxymaleic acid), and sodium fluoride (to a concentration of 0·05M) was adjusted to pH 6·5, covered with a layer of toluene and stored at 20°. After 72 hours, the solution (pH 6·8) was heated on the boiling-water bath for 10 minutes to inactivate the enzymes, and coagulated protein was removed on the centrifuge. The clear supernatant liquid was evaporated under reduced pressure at room temperature to a solid mass (A). A small sample of the residue was examined on paper chromatograms for sugar and sugar phosphate, by a variety of solvent systems (for methods see Partridge, *Biochem. J.*, 1948, **42**, 238; Hough, Jones, and Wadman, *J.*, 1950, 1702; Hanes and Isherwood, *Nature*, 1949, **164**, 1107; Benson *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 1710). In this manner, ketopentose, hexoses, hexose diphosphate, and free phosphate were detected, but neither heptulose nor pentose phosphate. The ketopentose was recognised on the paper chromatogram from its rate of movement, which is more rapid than that of any one of the aldopentoses, and from the characteristic blue colour obtained on spraying the chromatogram with a solution of resorcinol and hydrochloric acid in butanol, followed by careful heating. Further experiments showed that reaction for 24 hours only at room temperature gave pentose phosphate, since on paper chromatograms a spot was obtained close to hexose diphosphate which gave a positive reaction for phosphate with Hanes and Isherwood's molybdate reagent (*loc. cit.*) and a positive test for pentose (red colour) with the *p*-anisidine hydrochloride reagent (Hough, Jones, and Wadman, *loc. cit.*).

The residue (A) was extracted in the cold by vigorous shaking with absolute alcohol (3 × 200 c.c.). The brown extract was filtered, de-ionised by Amberlite Resins IR-4B and IR-100, and concentrated under reduced pressure at room temperature to a brown syrup (1·01 g.). This syrup was transferred to a column of powdered cellulose (1½ × 16″) and subjected to partition chromatography with butanol nearly saturated with water as the mobile phase (for method, see Hough, Jones, and Wadman, *J.*, 1949, 2511), to give, on evaporation of the appropriate portion of the effluent, a fraction (62·6 mg.) containing the ketopentose and a little ribose (as indicated by paper chromatography). This mixture was refractionated by partition chromatography, but this time on two sheets of Whatman No. 1 filter paper (22½ × 18¼″) with butanol–ethanol–water (40 : 11 : 19 parts v/v) as mobile phase. After separation, the papers were air-dried at room temperature, and the sugars located by the use of test strips (Flood, Hirst, and Jones, *J.*, 1948, 1679), and then extracted with methanol–water (micro-Soxhlet). Evaporation under reduced pressure gave fraction A {43 mg.; $[\alpha]_D$ −12·5° (*c*, 1·3 in water)}, containing the ketopentose, and fraction B (7·5 mg.), a mixture of ribose and ketopentose. The ketopentose moved at the same rate on the paper chromatogram as xyloketose (R_F 0·28; standard, rhamnose R_F 0·30) in both butanol–pyridine–water (10 : 3 : 3 parts v/v), where riboketose (R_F 0·26) moves slightly slower, and ethyl acetate–acetic acid–water (9 : 2 : 2 parts v/v) in which riboketose is slightly faster. Epimerisation of a small portion of the ketopentose in either pyridine at 100° for 3 days or dilute aqueous ammonia at 37° for a week or more gave, as shown by paper chromatography, xylose along with traces of ribose and arabinose. Under these conditions, the same result was obtained with an authentic specimen of D-xyloketose prepared by heating D-xylose in pyridine (Levene and Tipson, *J. Biol. Chem.*, 1930, **115**, 731) and separating the products by partition chromatography. Reaction of the ketopentose (38 mg.) in water (2 c.c.) with phenylhydrazine (0·2 c.c.) and acetic acid (0·2 c.c.) at 60—70° for 3 hours afforded a crystalline pentosazone which was filtered off, washed with a little benzene, recrystallised from ethanol–water, and dried at 60° under reduced pressure (*ca.* 40 mg.; m. p. 165—167°; mixed m. p. with L-xylosazone 190—192°, with D-xylosazone 161°, and with L- or D-ribosazone 161°; m. p. of crystals prepared from equimolecular proportions of the pentosazone and L-xylosazone, 202—203°; authentic DL-xylosazone had m. p. 207°). The pentosazone showed a rise in mutarotation from $[\alpha]_D^{21}$ −19° (*c*, 0·72 in ethanol, 1 hour) to −31°±3° (equil. value; 48 hours); similarly, D-xylosazone exhibits mutarotation in ethanol {$[\alpha]_D^{21}$ −15° (*c*, 0·44) ⟶ −39°±3° (equil. value; 48 hours) (cf. Levene and La Forge, *loc. cit.*; Fischer, *loc. cit.*)}. The crystalline form of the pentosazone was, microscopically, typical of xylosazone and different from that of ribosazone (cf. Hassid and McCready, *Ind. Eng. Chem.*, 1942, **14**, 683). On recrystallisation from benzene, the pentosazone (m. p. 157°) showed $[\alpha]_D^{21}$ −16° (*c*, 0·32 in ethanol; initial value) ⟶ −43°±3° (48 hours; const.) (Found: C, 62·2; H, 7·1; N, 17·4. $C_{17}H_{20}O_3N_4$ requires C, 62·2; H, 6·1; N, 17·1%). Authentic D-xylosazone on crystallisation

from benzene showed $[\alpha]_D^{19}$ $-26° \longrightarrow -46° \pm 3°$ (*c*, 1·98 in alcohol). Attempts to isolate the osatriazole were unsuccessful, presumably because of the small quantity of osazone available. Efforts to prove conclusively the identity of this osazone by *X*-ray analysis proved abortive.

Two control experiments, involving in one the enzyme preparation and hexose diphosphate at pH 6·5, and in the other glycollic aldehyde and the enzyme preparation at pH 6·5, were treated as described above. In neither case was ketopentose produced but, in the experiment involving hexose diphosphate and the enzyme, paper chromatography indicated the presence of ribose, glucose, fructose, and galactose(?).

In another experiment, glycollic aldehyde was kept in aqueous solution with dihydroxyacetone at pH 6·5, and tests for pentose (furfuraldehyde method) were applied at intervals; pentose was not produced. Addition of the enzyme preparation to this mixture did not lead to the formation of pentose.

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THE UNIVERSITY, BRISTOL. [*Received, July 14th*, 1952.]

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773. *The Synthesis of Sugars from Simpler Substances. Part IV.* Enzymic Synthesis of 6-Deoxy-D-fructose and 6-Deoxy-L-sorbose.*

By L. HOUGH and J. K. N. JONES.

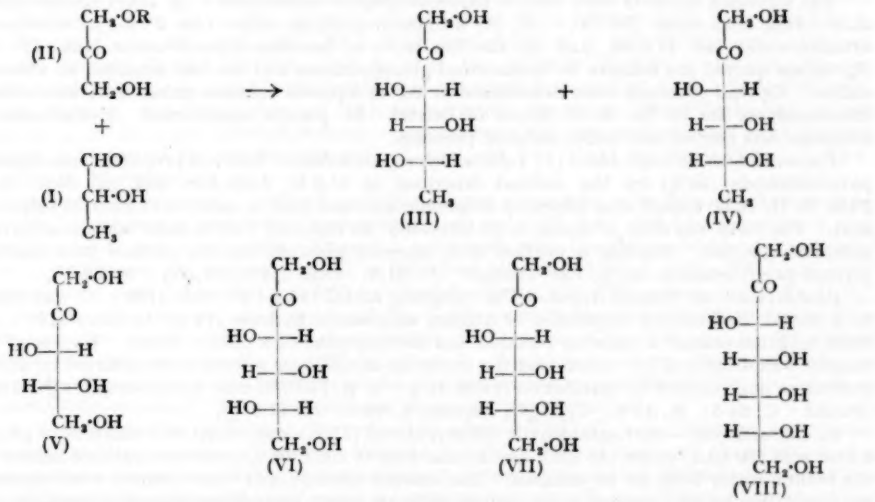
In the presence of an enzyme preparation from peas, DL-lactaldehyde combines with triose phosphate, to give optically active methyl pentose sugars. From the reaction mixture, 6-deoxy-D-fructose and 6-deoxy-L-sorbose have been isolated and characterised. The significance of these observations is discussed.

THE methyl pentose (6-deoxyhexose) sugars are of common occurrence in Nature, although they have always been found in the combined form linked glycosidically to some other fragment. Thus L-rhamnose (6-deoxy-L-mannose) occurs in a variety of plant materials combined either with other monosaccharides as in the gums and mucilages (Hirst and Jones, *Research*, 1951, **4**, 411) or with flavones, anthocyanins, or other aglycones. L-Fucose (6-deoxy-L-galactose) also is encountered in plant materials as, for example, in gum tragacanth (James and Smith, *J.*, 1945, 744) and occurs in polysaccharides of animal origin such as the blood-group substances (Aminoff, Morgan, and Watkins, *Biochem. J.*, 1950, **46**, 426); it is a common constituent of marine algæ. Other methyl pentoses are more rarely encountered; of these, D-fucose and D-quinovose (6-deoxy-D-glucose) occur in Jalep resin (Votoček, *Ber.*, 1910, **43**, 476), while several other methyl pentoses occur as methoxy- or deoxy-derivatives in cardiac glycosides (Elderfield, *Adv. Carbohydrate Chem.*, 1945, **1**, 147), the methoxy- and deoxy-group invariably being situated at $C_{(3)}$ and $C_{(2)}$ respectively.

Nothing is known concerning the origin of these methyl pentoses in Nature, although the most obvious suggestion is that they arise by reduction of the $C_{(6)}$-hydroxyl group of a hexose, but this is improbable since, amongst other objections, L-mannose, the precursor of L-rhamnose, is not known to occur in Nature. A further possibility envisages the combination by aldol-type condensation, either of two triose units, lactaldehyde (I) and dihydroxyacetone (II; R = H), or of acetaldehyde with two molecules of glycollic aldehyde or one molecule of tetrose (cf. Votoček, *Bull. Soc. chim.*, 1928, **43**, 1; Hough and Jones, *Nature*, 1951, **167**, 180). In order to test the second of these hypotheses, the condensation of DL-lactaldehyde with dihydroxyacetone in the presence of lime-water was attempted and it was observed that sugars moving on paper chromatograms at the rate of 6-deoxyketohexoses and showing the same colour reactions were produced (Hough and Jones, unpublished results) (DL-lactaldehyde was prepared from 1 : 1-dibutoxypropan-2-one by reduction with lithium aluminium hydride, followed by hydrolysis with dilute formic acid of the resultant 1 : 1-dibutoxypropan-2-ol). Accordingly, the enzymic synthesis of methyl

* Part III, preceding paper.

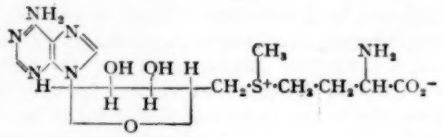
pentose was attempted by allowing a mixture of DL-lactaldehyde (I), the disodium salt of D-fructose-1 : 6 diphosphate and a crude aldolase preparation from peas to stand at pH 6·5. Under the influence of pea aldolase, fructose diphosphate is split into dihydroxyacetone phosphate (II; R = PO_3H_2) and D-glyceraldehyde-3 phosphate (Stumpf, *J. Biol. Chem.*, 1948, **176**, 233; Tewfik and Stumpf, *Amer. J. Bot.*, 1949, **36**, 567). This reaction is reversible: thus, D-frucose-1 : 6 diphosphate may be regenerated or the dihydroxyacetone phosphate may combine with lactaldehyde (I), to give a 6-deoxy-2-ketohexose-1 phosphate. It was observed chromatographically that considerable quantities of two 6-deoxyketohexoses were produced. After inactivation of the enzyme by heat, the solution was filtered, and the filtrate passed through a column of Amberlite resin IR-120 to remove cations. The resultant acidic solution was heated to hydrolyse phosphate esters, and then completely de-ionised by passage through a column of Amberlite resin IR-4B, and the effluent concentrated to a syrup. The sugar mixture was subjected to partition chromatography on a column of cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511), two optically active fractions being obtained with the properties of 6-deoxy-2-ketohexoses. The first fraction crystallised on nucleation with a specimen of 6-deoxy-L-sorbose (Müller and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 263), from which it was indistinguishable chromatographically and by mixed melting point and optical rotation. Its osazone was identical with that prepared from authentic 6-deoxy-L-sorbose (III). The second fraction was obtained as a syrup showing properties in accordance with those of 6-deoxy-D-fructose (IV). Confirmation of this identity was obtained by conversion into crystalline 2 : 3-*iso*propylidene 6-deoxy-D-fructose (Morgan and Reichstein, *ibid.*, p. 1023), and by formation of the phenylosasazone which was indistinguishable by *X*-ray analysis from its enantiomorph, L-rhamnosazone. No trace of any other 6-deoxyketohexose or 6-deoxyaldohexose was detected.



It has already been observed (Meyerhof, Lohmann, and Schuster, *Biochem. Z.*, 1936, **286**, 301, 319) that D- and L-glyceraldehyde condense with dihydroxyacetone phosphate in the presence of aldolase to give the 1-phosphate of D-fructose (VII) and L-sorbose (VI) respectively, and it is clear that D- and L-lactaldehyde condense with dihydroxyacetone in an analogous manner. It is also significant that glycollic aldehyde condenses with triose phosphate under the influence of aldolase to give D-xylulose (Hough and Jones, preceding paper). In all these ketoses (III, IV, V, VI, VII) produced by condensation of an aldehyde with dihydroxyacetone phosphate in the presence of aldolase, the stereochemical configuration on $C_{(3)}$ and $C_{(4)}$ is the same, that is, they are all $C_{(5)}$ derivatives of D-xylulose (V).

One would expect, therefore, that, under these conditions, D-erythrose would condense with dihydroxyacetone phosphate to give D-altroheptulose (sedoheptulose), and it is precisely this sugar which was obtained by Horecker and Smyrniotis (*J. Amer. Chem. Soc.*, 1952, **74**, 2123; cf. Benson *et al.*, *J. Biol. Chem.*, 1952, **196**, 703).* It will be of interest to see if the 5-deoxy-2-ketopentose resulting from the condensation of acetaldehyde and dihydroxyacetone phosphate (Meyerhof, Lohmann, and Schuster, *loc. cit.*) has the D-xylulose configuration.

Although lactaldehyde can give rise to methyl pentoses, it is evident that this route will explain neither the presence in natural products of the common sugar L-rhamnose, nor the presence of L-fucose unless, in the latter case, isomerisation at $C_{(3)}$ of the 6-deoxy-L-sorbose is postulated. Clearly, other enzyme systems and other modes of origin of this class of sugar will require investigation. In this connection, the observation of Cartori (*J. Amer. Chem. Soc.*, 1952, **74**, 2942) that adenosine triphosphate participates in enzymic transmethylation reactions involving methionine as methyl donor, by formation of orthophosphate and *S*-adenosylmethionine (IX), is of interest. The latter compound is a possible precursor of 5-deoxy-5-methylthio-D-ribose, and this mechanism may also be operative in the biogenesis of other methyl pentoses and 2-deoxy-sugars.

(IX) 

Experimental

The following solvents were used in chromatographic separations: (*a*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4), (*b*) *n*-butanol–pyridine–water (10 : 3 : 3), (*c*) *n*-butanol–ethanol–water (40 : 11 : 19), and (*d*) the top layer of benzene–ethanol–water (169 : 47 : 15). R_G values quoted are relative to tetramethyl glucopyranose and are not intended as absolute values. Optical rotations were determined at 20° in aqueous solution unless otherwise stated. Microanalyses are by Mr. B. S. Noyes of Bristol. M. p.s are uncorrected. Evaporation of solutions was carried out under reduced pressure.

Pyruvaldehyde Dibutyl Acetal (1 : 1-*Dibutoxypropan*-2-*one*).—This was prepared from aqueous pyruvaldehyde (30%) by the method described in U.S.P. 2,421,559/1947 (cf. *Brit. Abs.*, 1950, B, II, 1033) except that toluene-*p*-sulphonic acid was used as catalyst in place of sulphuric acid. The yield was 60 g. of acetal, b. p. 100—105°/16 mm., n_D^{20} 1·4200, from 300 c.c. of pyruvaldehyde solution. Heating a portion with aqueous phenylhydrazine acetate gave methylglyoxal phenylosazone, m. p. 153° (Found: N, 21·5. Calc. for $C_{15}H_{16}N_4$: N, 22·2%).

DL-*Lactaldehyde Dibutyl Acetal*.—The foregoing acetal (55 g.) in ether (150 c.c.) was added to a cooled, well-stirred suspension of lithium aluminium hydride (14 g.) in ether (100 c.c.). Each addition caused a vigorous reaction and development of a yellow colour. Excess of the reagent was destroyed by water, and the crude DL-*lactaldehyde dibutyl acetal* isolated by ether-extraction and purified by distillation [yield 41 g.; b. p. 140°/16 mm. (bath-temp.), n_D^{20} 1·4262] (Found: C, 64·5; H, 12·1. $C_{11}H_{24}O_3$ requires C, 64·7; H, 11·8%).

DL-*Lactaldehyde*.—DL-Lactaldehyde dibutyl acetal (15 g.) was added to a mixture of glacial acetic acid (30 c.c.), water (40 c.c.), and formic acid (1 c.c.; 98%), and the mixture heated on the boiling-water bath for 30 minutes. The solvent mixture and butyl alcohol were removed by distillation at 40°, leaving a viscous oil with an odour resembling that of glyceraldehyde (4·8 g.). This crystallised in part. The crystals were filtered off and washed with ether and had m. p. 107° (Found: C, 48·8; H, 8·0. Calc. for $C_3H_6O_3$: C, 48·6; H, 8·1%). Heating with alcoholic *p*-nitrophenylhydrazine gave DL-lactaldehyde *p*-nitrophenylhydrazone, m. p. 112° (Found: N, 18·4. Calc. for $C_9H_{11}O_3N_3$: N, 20·2%). Lactaldehyde reduces hot Fehling's solution and yields acetaldehyde on oxidation with sodium metaperiodate solution. Its movement (R_G 0·60) in solvent (*b*) is faster than that of rhamnose (R_G 0·30 assumed), and it gives a yellow colour with the *p*-anisidine hydrochloride spray (Hough, Jones, and Wadman, *loc. cit.*).

* *Added in Proof*.—Sedoheptulose has now been isolated from the condensation of D-erythrose and hexose diphosphate in the presence of a crude pea aldolase preparation (Hough and Jones, unpublished results).

Synthesis of Methyl Pentose.—Hexose diphosphate (sodium salt; 9 g.) was dissolved in water (50 c.c.), and DL-lactaldehyde (4·8 g.) in water (25 c.c.) added. A solution (150 c.c.) of aldolase from peas (50 g.), prepared as described in Part III (*loc. cit.*), was then added and, after mixing, the surface of the solution was covered with a layer of toluene. The pH of the solution at this stage was 6·5. After 72 hours at 20°, examination of the solution on the paper chromatogram (solvent *a*) showed the presence of hexose, pentose, and 6-deoxyketohexose. The solution (pH 6·5) was heated at 90° for 30 minutes to inactivate enzymes, and filtered. The cooled solution was then passed through a column of Amberlite resin IR-120 to remove cations. The acidic effluent (pH *ca.* 1·0) was then heated at 90° for 8 hours to hydrolyse any phosphate esters present, cooled, and de-ionised by passage through a column of Amberlite resin IR-4B. The effluent (pH 7·5) was acidified with acetic acid (2 c.c.) and evaporated to a syrup which was dissolved in aqueous methanol. Excess of acetone was added to this solution, and the precipitate discarded. Concentration of the filtered solution gave a brown syrup [A; 2·63 g.; $[\alpha]_D$ −11° (*c*, 4·0)]. A portion of this material was examined on the paper chromatogram with solvent (*a*). After the paper had been sprayed with the *p*-anisidine hydrochloride spray and then heated, coloured spots indicating the presence of lactaldehyde (yellow, weak), two 6-deoxyketohexoses (yellow, strong), ribose (red, weak), fructose (yellow, medium), arabinose (red, weak), and galactose(?) (brown, weak) were detected. Solvent (*d*) gave the best separation of the two deoxyketohexoses, moving them 17 and 9·2 cm. respectively in 72 hours. They gave red colours with the resorcinol spray.

Separation and Identification of 6-Deoxy-L-sorbose and 6-Deoxy-D-fructose.—A portion (1 g.) of (A) (above) in acetone (2 c.c.) was placed on the top of a column of cellulose [Whatman cellulose powder, standard grade, previously washed with solvent (*d*)]. Solvent (*d*; 1·5 l.) was passed down the column, followed by pure *n*-butanol, the effluent being collected portionwise by means of an automatic fraction cutter (Hough, Jones, and Wadman, *loc. cit.*). Examination of the effluent on paper chromatograms showed that the two 6-deoxyketohexoses had been completely separated, and evaporation of the appropriate tubes of effluent gave fraction 1 (0·25 g.), $[\alpha]_D$ −21° (*c*, 0·43) which crystallised on nucleation with 6-deoxy-L-sorbose (Müller and Reichstein, *loc. cit.*). The crystals, recrystallised from acetone–light petroleum (b. p. 60—80°), had m. p. 88°, $[\alpha]_D^{22}$ −25°±2° (*c*, 0·72), and mixed m. p. with an authentic specimen 88—89° (Found: C, 43·7; H, 7·9. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·3%). Its rate of movement in solvents (*a*), (*b*), and (*c*), relative to that of rhamnose, was 1·24, 1·36, 1·34 respectively, values identical with those obtained with an authentic specimen. Phenylhydrazine acetate solution at 70° (3 hours) afforded 6-deoxy-L-gulosazone which was recrystallised from aqueous ethanol and dried at 60° *in vacuo* (Found: C, 43·7; H, 7·9. Calc. for $C_{18}H_{22}O_3N_4$: C, 43·9; H, 7·4; N, 16·4%).

Fraction 2 {0·7 g.; $[\alpha]_D$ −13°±2° (*c*, 1·8)} did not crystallise. Its rate of movement in solvents (*a*), (*b*), and (*c*) relative to that of rhamnose was 1·22, 1·39, and 1·20 respectively, and corresponded to 6-deoxyfructose. It gave a red colour with the resorcinol–hydrochloric acid spray. 6-Deoxy-D-glucosazone, formed as described above, had m. p. 176—178°, $[\alpha]_D$ −59° (1 hour) ⟶ −53°±3° (const.; *c*, 0·73 in ethanol) (Found: N, 16·7. Calc. for $C_{18}H_{22}O_3N_4$: N, 16·4%). The osazone on *X*-ray crystallographic examination was indistinguishable from 6-deoxy-L-glucosazone (L-rhamnosazone) which had m. p. 176—178°, $[\alpha]_D$ +80° (initial value) ⟶ +60°±3° (const.; *c*, 0·57 in ethanol). Analysis by paper chromatography of the products produced when the deoxyketohexose was heated in pyridine at 100° for 7 days in a sealed tube indicated that quinovose and rhamnose were produced.

2 : 3-iso*Propylidene* 6-*Deoxy*-D-*fructose*.—The sugar (0·38 g.) was dissolved in acetone (25 c.c.) containing gaseous hydrogen chloride (0·5 g.). After 1 hour, an examination of a portion of the solution on the paper chromatogram (solvent *b*) indicated that 6-deoxy-D-fructose was no longer present as such; in its place a faster-moving spot (R_G *ca.* 1·0) was observed. After 3 hours, the solution was neutralised with silver carbonate, then filtered, and the filtrate concentrated. On nucleation of the syrup (0·3 g.) with 2 : 3-*iso*propylidene 6-deoxy-D-fructose (Morgan and Reichstein, *loc. cit.*) crystallisation rapidly took place. The product had m. p. 112° and mixed m. p. (with an authentic specimen, m. p. 114°) 113°, after recrystallisation from ether–light petroleum (b. p. 60—80°), $[\alpha]_D$ +8° (*c*, 1·2 in ethanol) (Found: C, 52·9; H, 7·8. Calc. for $C_9H_{16}O_5$: C, 53·0; H, 7·8%).

The authors thank the Chemical Society for a grant and Professor T. Reichstein for the gift of several crystalline sugars, which considerably facilitated the work described above.

THE UNIVERSITY, BRISTOL. [*Received, July 14th*, 1952.]

774. *Alternaric Acid. Part I. Purification and Characterisation.*

By JOHN FREDERICK GROVE.

Alternaric acid, $C_{21}H_{30}O_8$, a phytotoxic metabolite of *Alternaria solani*, is an optically inactive unsaturated dibasic acid. Its ultra-violet and infra-red absorption spectra and other evidence show that one of the acidic functions is due to the presence of a β-dicarbonyl grouping.

THE production by certain strains of *Alternaria solani* (Ell. and Mart.) Jones and Grout of a substance with remarkably specific antifugal activity but low antibacterial properties has been described by Brian, Curtis, Hemming, Unwin, and Wright (*Nature*, 1949, **164**, 534). The active compound, alternaric acid, is markedly phytotoxic and it is possible that it is, at least in part, responsible for plant diseases caused by *A. solani* (Brian, Elson, Hemming, and Wright, *Ann. Appl. Biol.*, in the press; cf. Pound and Stahmann, *Phytopathology*, 1951, **41**, 30). Isolation of the acid has been described by Brian, Curtis, Hemming, Jefferys, Unwin, and Wright [*J. Gen. Microbiol.*, 1951, **5**, 619; cf. Darpoux, Faivre-Amiot, and Roux (who used a different method of extraction), *Compt. rend.*, 1950, **230**, 993; *Compt. rend. Acad. Agric.*, 1949, **35**, 266].

Alternaric acid, $C_{21}H_{30}O_8$, m. p. 138°, is a highly crystalline, colourless, optically inactive, unsaturated dibasic acid; it contains no methoxyl groups, and forms a monohydrate, m. p. 135°. It is unchanged in hot water but was immediately hydrolysed by boiling dilute mineral acids or sodium hydroxide. Acid hydrolysis rapidly gave one molecule of carbon dioxide with some indications of the liberation of a second molecule, whereas alkaline hydrolysis gave a number of volatile products including acetone. A complex mixture of acidic products remained in each case, as yet unidentified.

TABLE 1. *Infra-red absorption.*

Compound	Absorption frequency (cm.$^{-1}$) C=C	C=O	OH
Alternaric acid	1650	1710, 1732	3150, 3430
Alternaric acid monohydrate	1650	1710, *ca.* 1727	2490, 2610, 3480
Methyl alternarate	1650	1710, 1738	3500

TABLE 2. *Ultra-violet absorption.*

Solvent	Alternaric acid $\lambda_{max.}$	Alternaric acid log ε	Methyl alternarate $\lambda_{max.}$	Methyl alternarate log ε
0·1N-NaOH	271, 250	4·14, 4·17	273, 250	4·10, 4·17
Water	273, ~253, ~210	4·04, 3·83, 4·06	—	—
Ethanol	274, ~210	4·04, 4·07	273, ~252, ~210	4·05, 3·88, 3·98
Methanol + 5% of HCl	273, ~210	3·99, 3·99	273, ~210	4·06, 4·08

The infra-red spectrum of solid anhydrous alternaric acid (Table 1) showed two bands in the C=O stretching region, and two weak bands due to OH groups in the 3-μ region. The spectrum of the monohydrate was almost identical between 7 and 14 μ but showed marked differences in the C=O and OH stretching regions.

The effect of varying the pH of the medium on the ultra-violet absorption of alternaric acid is shown in Table 2. The position of the main absorption band of alternaric acid at 273 mμ is unaffected, but in alkaline solution a second absorption band appears at 250 mμ. Inflexions in the curves at this point were observed when alternaric acid was examined in aqueous or in ethanolic solutions.

Alternaric acid titrated as a dibasic acid but the potentiometric titration curve showed only one point of inflexion. Heating with excess of 0·1N-sodium hydroxide followed by back titration failed to disclose additional acidity. Alternaric acid contains one carboxyl group as shown by a positive hydroxamic acid test and formation of a methyl ester on esterification with methanol and concentrated sulphuric acid; the second titratable acidic function is attributed to a β-dicarbonyl grouping, the presence of which is indicated by

characteristic colour reactions and by the formation of a chloroform-soluble copper complex. Although the orange colour with ferric chloride and the ready production of one molecule of carbon dioxide on acid hydrolysis suggested the presence of a tetronic acid grouping in alternaric acid, this is considered to be excluded by the ultra-violet and infra-red spectroscopic evidence (Herbert and Hirst, *Biochem. J.*, 1935, **29**, 1881; Duncanson, personal communication; Grove, unpublished results). Nevertheless, the presence of an enolic system is shown by the ultra-violet absorption spectra, and the peak at 250 mμ which appears in aqueous alkali but not in methanolic hydrochloric acid, in which enolisation and ionisation are suppressed, is attributed to the ionised enolic form of the β-dicarbonyl grouping.

The monomethyl ester of alternaric acid titrated as a monobasic acid, pK 4·35 (at 25°). It behaved similarly to alternaric acid in its colour reactions and ultra-violet absorption (Table 2). The infra-red spectrum (Table 1) also was similar to that of alternaric acid but showed only a single strong OH absorption. Both the acid and the methyl ester appear to be in the unenolised form in the solid state.

Zerewitinoff determinations in anisole showed the presence of four active hydrogen atoms in alternaric acid and three in the methyl ester. Thus, of the eight oxygen atoms in alternaric acid, four are contained in the carboxyl and β-dicarbonyl groupings and (probably) two in hydroxyl groups, leaving two, the function of which has not yet been determined.

In a microhydrogenation experiment with a palladium catalyst, alternaric acid absorbed hydrogen equivalent to the saturation of 3·6 double bonds and this figure undoubtedly includes the reduction of one or more carbonyl groups. Nevertheless, the behaviour of the acid towards bromine water and neutral permanganate in acetone, in conjunction with the infra-red and ultra-violet evidence, indicates the presence of (at least) one ethylenic bond; and it follows from the empirical formula and from what is known of the oxygen function that the presence of an aromatic ring is excluded.

Experimental

Microanalyses are by Drs. Strauss and Weiler, Oxford, and by Mr. W. Brown. M. p.s are corrected. The infra-red spectra were obtained with Nujol "mulls" in the apparatus described by Grove and Willis (*J.*, 1951, 877).

Alternaric Acid.—The crude yellow solid (m. p. 122—128°; 4·0 g.), obtained by chloroform-extraction of culture filtrates, previously adjusted to pH 3·5, of *A. solani* (strain 408) grown on sucrose–nitrate media (Brian *et al.*, *loc. cit.*, 1951) was taken up in hot benzene and a little amorphous insoluble material rejected. The solid which separated on cooling was twice recrystallised from dry benzene, giving a colourless product, m. p. 132° (2·7 g.). The bright yellow benzene mother-liquors were bulked and concentrated, to yield slighly less pure material, m. p. 130—132° (0·6 g.). The first fraction was dissolved in saturated sodium hydrogen carbonate solution (50 ml.) and extracted with ether (removing only a trace of gum); *alternaric acid* was then recovered by acidification of the bicarbonate solution with concentrated hydrochloric acid, dried *in vacuo* at room temperature, and crystallised twice from aqueous methanol. It formed colourless, thin, rectangular plates, m. p. 135—136° (2·4 g.), of the monohydrate (see below). For analysis, specimens were crystallised from absolute methanol or ethanol and formed elongated prisms, m. p. 138° [Found, on a sample dried *in vacuo* over phosphoric oxide (*a*) at 20°: C, 61·7, 61·6, 61·7, 61·6, 61·3; H, 7·5, 7·3, 7·6, 7·5, 7·3; OMe, 0; *C*-Me, 12·5%; equiv., 208, 199, 205, 205; *M* (Rast), 408. (*b*) At 80°: C, 61·5; H, 7·4. (*c*) At 100°: C, 61·3, 61·3; H, 7·3, 7·3. $C_{21}H_{30}O_8$ requires C, 61·4; H, 7·4; 3*C*-Me, 11·1; 4*C*-Me, 14·8%; equiv. (dibasic acid), 205; *M*, 410].

Alternaric acid crystallised from benzene in needles, m. p. 135° [Found, after drying *in vacuo* over phosphoric oxide (*a*) at 20°: C, 61·9, 62·0, 62·7, 62·4; H, 7·5, 7·3, 7·4, 7·3. (*b*) At 100°: C, 61·4; H, 7·7]. Specimens dried at room temperature gave high values for carbon due presumably to traces of adsorbed benzene; drying at 100° caused discoloration so that the agreement between the observed and the calculated analytical figures is perhaps fortuitous. The infra-red spectrum of alternaric acid crystallised from methanol or from carbon tetrachloride showed bands at 1560, 1338, 1292, 1270, *ca.* 1225, 1215, 1175, 1149, 1117, 1069, 1000, 975, 955, 932, *ca.* 910, 900, 820, 800, and 760 cm.$^{-1}$ in addition to those listed in Table 1.

Alternaric acid crystallised from water or aqueous methanol in colourless, thin, rectangular plates of the *monohydrate*, m. p. 135° [Found, dried at 20° *in vacuo* over concentrated sulphuric acid or phosphoric oxide: C, 58·8, 58·9, 59·0; H, 7·5, 7·7, 7·4%; equiv., 215. $C_{21}H_{30}O_8.H_2O$ requires C, 58·9; H, 7·5%; equiv., 214 (dibasic acid)]. The unit cell was orthorhombic with dimensions 49·96 × 5·778 × 7·754 Å. The density was 1·270 ± 0·003, whence the molecular weight (4 molecules per unit cell) is 428 ± 1. $C_{21}H_{32}O_9$ requires *M*, 428. The infra-red spectrum of the monohydrate closely resembled that of the anhydrous compound, but showed a strong band at 1240 cm.$^{-1}$ with a weaker absorption at 1214 cm.$^{-1}$ in place of the band at 1215 cm.$^{-1}$ with inflexion at 1225 cm.$^{-1}$, in addition to the differences in the C=O and OH stretching regions. The molecule of water of crystallisation was removed by phosphoric oxide *in vacuo* at 80° [Found: C, 61·2, 61·3; H, 7·2, 7·3; at 100°: C, 61·7, 61·5; H, 7·0, 7·6%; *M* (Rast), 435]. The infra-red spectrum of the material dehydrated at 80° was identical with that of anhydrous alternaric acid obtained by crystallisation from absolute methanol.

Zerewitinoff determination on anhydrous alternaric acid in anisole at 20° showed 1·01% active H; there was no further reaction at 80° ($C_{21}H_{30}O_8$ requires 4H, 0·98%).

On hydrogenation in acetic acid with a palladium catalyst, 5·100 mg. of alternaric acid took up 1·14 ml. of hydrogen at 27°/759 mm., corresponding to 3·6 double bonds.

Alternaric acid did not sublime at 130°/10^{-5} mm. and considerable discolouration and decomposition took place under these conditions. Alternaric acid was optically inactive (cf. Brian *et al.*, *loc. cit.*, 1951) {$[\alpha]_D^{14} \not> \pm 3°$ (*c*, 1·02 in acetone; *l* = 1 dm.); $[\alpha]_D^{16} \not> \pm 3°$ (*c*, 0·52 in chloroform; *l* = 4 dm.)}. Alternaric acid was only slightly soluble in cold water; it was very soluble in ethanol, methanol, pyridine, and chloroform, moderately soluble in benzene, ether, and carbon tetrachloride, and insoluble in light petroleum. Alternaric acid was recovered unchanged after 30 minutes' heating under reflux in aqueous solution. It dissolved in sodium hydrogen carbonate solution with evolution of carbon dioxide, and in sodium hydroxide. It gave the hydroxamic acid test (Feigl, "Qualitative Analysis by Spot Tests," 3rd Edn., Elsevier Publ. Co., Amsterdam, 1947, p. 357), a wine-red colour in methanol with titanous chloride solution, and a blue colour which faded rapidly when 5% aqueous titanous chloride solution was added to alternaric acid in methanol–pyridine and the solution shaken vigorously in air (Weygand and Csendes, *Ber.*, 1952, **85**, 45). A concentrated solution of alternaric acid in ethanol gave an orange colour with ferric chloride. Alternaric acid rapidly coupled with diazotised 5-chloro-*o*-toluidine in alkaline solution and formed a deep blue, chloroform-soluble copper complex on treatment with a solution of cupric acetate.

Alternaric acid dissolved in cold concentrated sulphuric acid to a colourless solution but charring took place on warming. It did not give a precipitate with 2 : 4-dinitrophenylhydrazine sulphate in methanol and decomposed when heated under reflux with Girard's reagent P in ethanol containing 10% acetic acid. It neither reduced Fehling's solution nor restored the colour to Schiff's reagent but reduced warm ammoniacal silver nitrate. Bromine water or 1% potassium permanganate solution in acetone was immediately decolourised at room temperature.

Methyl Alternarate.—To alternaric acid (0·40 g.) in methanol (10 ml.) at 0°, ice-cold concentrated sulphuric acid (1·0 ml.) was added with stirring. After 48 hours at 20° the yellow solution was poured into water (50 ml.), and the precipitated *ester* collected, dried, and recrystallised from methanol (0·28 g.) as colourless prisms, m. p. 106—107° (also from benzene) [Found: C, 62·2, 62·2, 62·2, 62·3; H, 7·4, 7·6, 7·5, 7·6; OMe, 7·8; active H, 0·77, 0·78%; equiv., 438; *M* (Rast), 435. $C_{22}H_{32}O_8$ requires C, 62·25; H, 7·6; OMe, 7·3; 3H, 0·71%; *M*, 424]; elongated plates, m. p. 103°, $[\alpha]_D^{21} \not> \pm 3°$ (*c*, 1·00 in acetone; *l* = 1 dm.), were obtained from aqueous methanol (Found: C, 62·4, 62·2; H, 7·4, 7·5; OMe, 7·1%; equiv., 414). Methyl alternarate was soluble in sodium hydroxide and liberated carbon dioxide from sodium hydrogen carbonate solution. Like the acid, it gave an orange colour with ferric chloride in ethanol, a wine-red colour with 5% titanous chloride in methanol, coupled with diazotised 5-chloro-*o*-toluidine, and formed a chloroform-soluble violet-blue copper complex with cupric acetate solution.

Acid Hydrolysis of Alternaric Acid.—Alternaric acid (98·0 mg.) was heated under reflux with 2N-sulphuric acid (10·00 ml.) in nitrogen at 130°, the issuing gases being passed through 0·1N-barium hydroxide. 1·16 Mols. of carbon dioxide were evolved in 2 hours, 1·25 mols. in 5 hours. Titration (N-sodium hydroxide) of the residue at 80° to a permanent end-point (slow dissolution of much oily material) disclosed that at the end of the reaction 2 potentially acidic groups were present, one possibly in a lactone ring. No volatile acids were detected on acidification and steam-distillation of this neutralised solution.

Action of Alkali on Alternaric Acid.—(a) 0·1N-NaOH *at* 90°. Alternaric acid (83·4 mg.),

titrated with 0·1027N-sodium hydroxide to phenolphthalein, consumed 3·97 ml. (equiv. wt., 205). 4·04 ml. of the alkali were then added and the solution heated at 90° for 1 hour, cooled, and back-titrated with 0·1025N-sulphuric acid to phenolphthalein; 4·05 ml. were required; thus alternaric acid does not contain a readily opened lactone ring. On the addition of concentrated hydrochloric acid to the neutral solution, alternaric acid (hydrate) was precipitated unchanged.

(*b*) N-NaOH *at* 100°. Alternaric acid (0·980 g.) and N-sodium hydroxide (20·48 ml.) were heated under reflux for 1 hour. No condensable gaseous products were evolved (solid carbon dioxide trap). A dark neutral oil rapidly separated and, on cooling and back-titration with 2N-sulphuric acid, 6·80 ml. were required, showing that an additional acid group had been formed during the hydrolysis. The solution was made just alkaline with 0·1N-sodium hydroxide and steam-distilled. From the neutral distillate ether removed 0·1 g. of a fragrant neutral oil. The aqueous solution yielded a dinitrophenylhydrazone (m. p. 118°; 0·1 g.; crystallised twice from ethanol), needles or plates, m. p. and mixed m. p. with authentic acetone dinitrophenylhydrazone, 124° [Found: C, 45·8; H, 4·3; N, 23·7%; *M* (Rast), 243. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·2; N, 23·5%; *M*, 238].

I am indebted to Mr. C. H. Unwin for supplies of crude alternaric acid and to Messrs. H. A. Willis and D. R. Holmes, Imperial Chemical Industries Limited, Plastics Division, for infra-red facilities and the *X*-ray measurements.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, BUTTERWICK RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS. [*Received, July 16th*, 1952.]

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775. *Internuclear Cyclisation. Part VI.* The Synthesis of Some Methyl-, Halogeno-, and Carbomethoxy-N-methylphenanthridones.*

By R. A. HEACOCK and D. H. HEY.

2-Amino-*N*-methylbenzo-*p*- and -*o*-toluidide, and 2-amino-4′-bromo-, 2-amino-4′-chloro-, 2-amino-2′-chloro-, and 2-amino-4-carbomethoxy-*N*-methylbenzanilide have been prepared. These six bases have been diazotised and the decomposition of the diazonium sulphates in aqueous solution and of the diazonium fluoroborates in acetone suspension has been studied. Substituted *N*-methylphenanthridones were obtained in each case except with 2-amino-2′-chloro-*N*-methylbenzanilide. The corresponding phenols accompanied the *N*-methylphenanthridones from the decomposition of the diazonium sulphates.

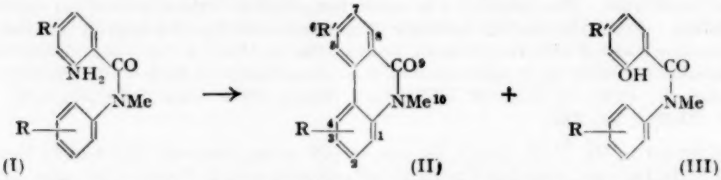
IN Part III (*J.*, 1952, 1508) methods were described by which *N*-methylphenanthridone could be obtained from *o*-amino-*N*-methylbenzanilide by successive diazotisation and elimination of nitrogen. The present communication describes the application of these methods to the preparation of certain methyl-, halogeno-, and carbomethoxy-*N*-methylphenanthridones, and an examination by chromatographic adsorption of the products formed in these reactions, undertaken to ascertain the scope and limitations of this synthetical approach to the phenanthridine system and to obtain information on the mechanism of the internuclear cyclisation process.

2-Amino-*N*-methylbenzo-*p*-toluidide (I; R = *p*-Me, R′ = H) was prepared by the reduction of *N*-methyl-2-nitrobenzo-*p*-toluidide, which was obtained both by the action of *o*-nitrobenzoyl chloride on methyl-*p*-toluidine and by the methylation of 2-nitrobenzo-*p*-toluidide. When an aqueous solution of the diazonium sulphate prepared from 2-amino-*N*-methylbenzo-*p*-toluidide was heated, nitrogen was evolved, and both 3 : 10-dimethylphenanthridone (II; R = 3-Me, R′ = H) and 2-hydroxy-*N*-methylbenzo-*p*-toluidide (III; R = *p*-Me, R′ = H) were formed. 3 : 10-Dimethylphenanthridone was also formed by the action of copper powder on the diazonium fluoroborate, prepared from 2-amino-*N*-methylbenzo-*p*-toluidide, together with a second compound, m. p. 193°. In similar manner 2-amino-*N*-methylbenzo-*o*-toluidide (I; R = *o*-Me, R′ = H) was prepared by the reduction of the corresponding nitro-compound, which was obtained by the two procedures outlined

* Part V, *J.*, 1952, 2276.

above for the isomeric benzo-*p*-toluidide. The action of heat on an aqueous solution of the diazonium sulphate gave 1 : 10-dimethylphenanthridone (II; R = 1-Me, R′ = H) and 2-hydroxy-*N*-methylbenzo-*o*-toluidide (III; R = *o*-Me, R′ = H); the former was also obtained by the action of copper powder on the diazonium fluoroborate in acetone.

Similarly both 4′-bromo- and 4′-chloro-*N*-methyl-2-nitrobenzanilide were converted into the corresponding amines (I; R = *p*-Br, R′ = H; and R = *p*-Cl, R′ = H), and decomposition of their diazonium fluoroborates in acetone gave 3-bromo- (II; R = 3-Br, R′ = H) and 3-chloro-10-methylphenanthridone (II; R = 3-Cl, R′ = H), respectively. The 4′-halogeno-*N*-methyl-2-nitrobenzanilides were prepared by the methylation of the



corresponding 4′-halogeno-2-nitrobenzanilides obtained from the action of *o*-nitrobenzoyl chloride on *p*-bromo- and *p*-chloro-aniline. 2′-Chloro-*N*-methyl-2-nitrobenzanilide, prepared both by the methylation of 2′-chloro-2-nitrobenzanilide and by the action of *o*-nitrobenzoyl chloride on *o*-chloro-*N*-methylaniline, gave on reduction the amine (I; R = *o*-Cl, R′ = H), which on diazotisation and subsequent heating gave only 2′-chloro-2-hydroxy-*N*-methylbenzanilide (III; R = *o*-Cl, R′ = H) and unidentified products.

4-Carbomethoxy-*N*-methyl-2-nitrobenzanilide was prepared by the action of 4-carbomethoxy-2-nitrobenzoyl chloride on methylaniline. Reduction to the corresponding base (I; R = H, R′ = CO_2Me), followed by diazotisation and the action of heat on the diazonium solution, gave both 6-carbomethoxy-10-methylphenanthridone (II; R = H, R′ = CO_2Me) and 4-carbomethoxy-2-hydroxy-*N*-methylbenzanilide (III; R = H, R′ = CO_2Me). Decomposition of the diazonium fluoroborate in acetone suspension by the addition of copper powder also gave 6-carbomethoxy-10-methylphenanthridone, but not the phenol.

With the limited range of substituted *o*-amino-*N*-methylbenzanilides so far used for the preparation of *N*-methylphenanthridones, it is not possible to discern any marked influence of the substituent atom or group on the yield in the cyclisation reaction apart from an indication of a low yield when the presence of an *ortho*-substituent limits the number of positions at which internuclear cyclisation can occur from two to one. The results so far reported are summarised below. Further discussion of the possible implications of these results must await investigations in which the nature and position of the substituent R is further varied.

Yields of the N-*methylphenanthridone obtained from* *o*-$NH_2{\cdot}C_6H_4{\cdot}CO{\cdot}NMe{\cdot}C_6H_4R$.

R	Diazonium sulphate method, %	Fluoroborate method, %
H	50	50
p-Me	50	49
o-Me	12	22
p-Br	—	33
p-Cl	—	44
o-Cl	0	—

Experimental

Dimethylphenanthridones.

N-*Methyl*-2-*nitrobenzo*-p-*toluidide*.—(*a*) To a solution of methyl-*p*-toluidine (10 g.) (Halberkann, *Ber.*, 1921, **54**, 1833) in pyridine (50 c.c.) was added slowly an ethereal solution of *o*-nitrobenzoyl chloride, prepared from the acid (12·2 g.) by Boëtius and Römisch's method (*Ber.*, 1935, **68**, 1924.) After removal of the ether, the solution was boiled for 5 minutes, cooled, and poured into water. The solid which separated was crystallised from benzene–light petroleum (b. p. 80–100°) and gave N-*methyl*-2-*nitrobenzo*-p-*toluidide* (15 g.) in hexagonal flat prisms, m. p. 105° (Found: C, 66·7; H, 5·3. $C_{15}H_{14}O_3N_2$ requires C, 66·7; H, 5·2%). (*b*) By the procedure

outlined above *o*-nitrobenzoyl chloride (from 20 g. of acid) and *p*-toluidine (12·9 g.) gave 2-nitrobenzo-*p*-toluidide (25·3 g.) in glistening plates, m. p. 147°, from aqueous alcohol (cf. Bellavita, *Gazzetta*, 1940, **70**, 584). A solution of the amide (20 g.) in a mixture of acetone (100 c.c.) and 20% aqueous sodium hydroxide (100 c.c.) was boiled under reflux with vigorous stirring, and methyl sulphate (40 c.c.) was added slowly. The mixture was then cooled and added to ice-water which was kept alkaline with 20% aqueous sodium hydroxide. An oil separated and solidified. Recrystallisation from benzene–light petroleum (b. p. 80—100°) gave *N*-methyl-2-nitrobenzo-*p*-toluidide (17·1) g. in prisms, m. p. 105—106°, identical with the product prepared by method (*a*).

N-*Methyl*-2-*nitrobenzo*-o-*toluidide*.—(*a*) A solution of toluene-*p*-sulphon-*o*′-toluidide (33·6 g.), prepared by Reverdin and Crepieux's method (*Ber.*, 1902, **35**, 1440), in 16% aqueous sodium hydroxide was warmed and methyl sulphate (25 c.c.) added. The mixture was kept alkaline with 16% aqueous sodium hydroxide. An oil separated and solidified. Recrystallisation from alcohol gave *N*-methyltoluene-*p*-sulphon-*o*′-toluidide (27 g.) in needles, m. p. 87°. Witt and Uerményi (*Ber.*, 1913, **46**, 302) recorded m. p. 119—120° for this compound, prepared by the action of toluene-*p*-sulphonyl chloride on methyl-*o*-toluidine, but Young (*J. Amer. Chem. Soc.*, 1934, **56**, 2783) gave m. p. 87—87·5° for the compound prepared by methylation of the sulphonanilide. Hydrolysis of *N*-methyltoluene-*p*-sulphon-*o*′-toluidide (26 g.) with concentrated sulphuric acid (30 c.c.) and acetic acid (15 c.c.), by the method used by Usherwood and Whiteley (*J.*, 1923, 1084) for the preparation of methyl-*o*-nitroaniline, gave methyl-*o*-toluidine (10·1 g.), b. p. 205—207°/760 mm. By the procedure described above for the corresponding derivative of *p*-toluidine, methyl-*o*-toluidine (10·1 g.) and *o*-nitrobenzoyl chloride (from 16·7 g. of acid) gave N-*methyl*-2-*nitrobenzo*-o-*toluidide* (8 g.) in prisms, m. p. 121—122°, from benzene–light petroleum (b. p. 80—100°) (Found: C, 66·5; H, 5·4%). (*b*) By the method used above with *p*-toluidine, *o*-nitrobenzoyl chloride (from 16·7 g. of acid) and *o*-toluidine (10·7 g.) gave 2-*nitrobenzo*-o-*toluidide* (21 g.) in needles, m. p. 174°, from alcohol (Found: C, 65·8; H, 4·5. $C_{14}H_{12}O_3N_2$ requires C, 65·6; H, 4·7%). Methylation of the nitrobenzotoluidide (20 g.), as in the preceding example, gave *N*-methyl-2-nitrobenzo-*o*-toluidide (18 g.) in needles, m. p. 122°, identical with the product prepared by method (*a*).

2-*Amino*-N-*methylbenzo*-p-*toluidide*.—A solution of the nitro-compound (10 g.) in alcohol (100 c.c.) and a suspension of Raney nickel (10 g.) in the same solvent were shaken with hydrogen at atmospheric pressure until the required quantity of hydrogen had been absorbed (2 hours). The suspension was filtered and the filtrate concentrated under reduced pressure. Recrystallisation of the solid which separated gave 2-*amino*-N-*methylbenzo*-p-*toluidide* (7·6 g.) in elongated prisms, m. p. 64—65°, from light petroleum (b. p. 40—60°) (Found: C, 75·2; H, 6·4. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7%).

2-*Amino*-N-*methylbenzo*-o-*toluidide*.—In similar manner the corresponding nitro-compound (10 g.) gave 2-*amino*-N-*methylbenzo*-o-*toluidide* (8 g.), which separated from benzene–light petroleum (b. p. 80—100°) in prisms, m. p. 99—100° (Found: C, 74·7; H, 6·7%).

Decomposition of the Diazonium Sulphate prepared from 2-*Amino*-N-*methylbenzo*-p-*toluidide*.—The amine (2·5 g.) was diazotised in concentrated sulphuric acid (10 c.c.) and water (100 c.c.) by the addition of sodium nitrite (1 g.) in water (10 c.c.), and after filtration the solution was heated on a boiling-water bath for 1 hour. The cold mixture was extracted with chloroform, and the extract was washed several times with 10% aqueous sodium hydroxide. Concentration of the dried (Na_2SO_4) chloroform extract gave a brown tar (1·5 g.), which was dissolved in benzene–light petroleum (b. p. 60—80°) (3 : 1) and adsorbed on an alumina column (20 × 2 cm.). Washing of the column with the same mixed solvent (1000 c.c.) gave a yellow solid, which on recrystallisation gave 3 : 10-*dimethylphenanthridone* (1·11 g.) in long prisms, m. p. 136—137°, from benzene–light petroleum (b. p. 80—100°) (Found: C, 80·7; H, 5·7. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8%). Subsequent successive elution with benzene, benzene–ether, and ether gave, first, a yellow solid (0·1 g.), m. p. 120—140°, and then brown tars. Acidification of the alkaline extract liberated a brown tar (1·1 g.) which was dissolved in benzene and adsorbed on a column of silica gel (10 × 2 cm.). Elution with benzene (400 c.c.) gave a white solid, which yielded 2-*hydroxy*-N-*methylbenzo*-p-*toluidide* (0·5 g.) in needles, m. p. 90—91°, from light petroleum (b. p. 80—100°) (Found: C, 74·7; H, 6·3. $C_{15}H_{15}O_2N$ requires C, 74·5; H, 6·2%).

Decomposition of the Diazonium Fluoroborate prepared from 2-*Amino*-N-*methylbenzo*-p-*toluidide*.—The amine (2 g.) was diazotised in concentrated sulphuric acid (10 c.c.) and water (30 c.c.) with sodium nitrite (1 g.) in water (10 c.c.), and to the filtered solution, cooled to 0°, sodium fluoroborate (5 g.) in water (10 c.c.) was added slowly with stirring. After ½ hour the yellow diazonium fluoroborate, which had separated, was collected and dried *in vacuo*. To a

suspension of the dry fluoroborate in " AnalaR " acetone (50 c.c.) copper powder * (2 g.) was added. There was a vigorous evolution of nitrogen, and the reaction was complete within ½ hour. The mixture was filtered into cold water, the residue being extracted successively with hot acetone and boiling water. The combined aqueous and acetone solutions were extracted with chloroform, and the extract was washed with 10% aqueous sodium hydroxide. Concentration of the dried (Na_2SO_4) chloroform solution gave a yellow solid (2 g.), which was dissolved in benzene–light petroleum (b. p. 60—80°) (3 : 1) and adsorbed on an alumina column (20 × 2 cm.). Elution with the same solvent and then with benzene (900 c.c.) gave 3 : 10-dimethylphenanthridone (0·9 g.) in prisms, m. p. 136—137°, from benzene–light petroleum (b. p. 80—100°). There was no depression in m. p. on admixture of the specimen with the corresponding product prepared from the diazonium sulphate. Further elution with benzene–ether (3 : 1) (1000 c.c.) gave another *substance* as pale yellow prisms (0·6 g.), m. p. 193°, from benzene (Found: C, 79·7; H, 6·4; N, 6·4%; *M*, 244), and finally a brown tar. Acidification of the alkaline extract gave only a trace of a black tar.

Decomposition of the Diazonium Sulphate prepared from 2-Amino-N-methylbenzo-o-toluidide.—The amine (3·5 g.) was diazotised in sulphuric acid, the solution was heated, and the products were worked up and purified as described above for the corresponding reaction with the benzo-*p*-toluidide. The brown tar (1·1) g. from the neutral chloroform extract gave 1 : 10-*dimethylphenanthridone* (0·4 g.) in needles, m. p. 141—142°, from light petroleum (b. p. 80—100°) (Found: C, 80·3; H, 6·1%). Further elution with benzene (2500 c.c.) gave a *substance* as pale yellow prisms (0·3 g.), m. p. 165° [from benzene–light petroleum (b. p. 80—100°)] (Found: C, 75·3; H, 5·7; N, 5·9%; *M*, 224). Acidification and extraction of the alkaline washings gave, by the procedure described above, *2-hydroxy-N-methylbenzo-o-toluidide* (0·52 g.) in needles, m. p. 99° (Found: C, 74·5; H, 6·6%).

Decomposition of the Diazonium Fluoroborate prepared from 2-Amino-N-methylbenzo-o-toluidide.—The diazonium fluoroborate, prepared from the amine (3·5 g.), was decomposed and the product worked up as described above for the corresponding reaction with the benzo-*p*-toluidide. The orange gum (3·4 g.), obtained from the neutral chloroform solution, was adsorbed on alumina from benzene–light petroleum (b. p. 60—80°) (1 : 1). Elution with benzene–light petroleum (b. p. 60—80°) (2 : 1) (2000 c.c.) gave 1 : 10-dimethylphenanthridone (0·75 g.) in needles, m. p. 141—142°, from light petroleum (b. p. 80—100°), identical with the product obtained from the diazonium sulphate. Further elution with various solvents gave only unidentified tars. Acidification of the alkaline washings gave only a trace of a brown gum.

Halogeno-N-methylphenanthridones.

Halogeno-2-nitrobenzanilides.—An ethereal solution of *o*-nitrobenzoyl chloride (prepared from 20 g. of the acid) was added slowly with cooling to a solution of *p*-bromoaniline (20 g.) in pyridine (100 c.c.). The ether was evaporated and the pyridine solution was boiled for 5 minutes, cooled, and poured into water. Crystallisation of the separated solid from alcohol–acetone gave *4′-bromo-2-nitrobenzanilide* (29 g.) in needles, m. p. 200—201° (Found: C, 48·7; H, 3·1. $C_{13}H_9O_3N_2Br$ requires C, 48·6; H, 3·1%). In similar manner *o*-nitrobenzoyl chloride (from 20 g. of acid) and *p*-chloroaniline (15·4 g.) gave *4′-chloro-2-nitrobenzanilide* (27 g.), which separated from alcohol in needles, m. p. 182—183° (Found: C, 56·5; H, 3·4. $C_{13}H_9O_3N_2Cl$ requires C, 56·5; H, 3·3%). From *o*-chloroaniline (15·4 g.) in place of *p*-chloroaniline, *2′-chloro-2-nitrobenzanilide* (14 g.) was obtained in needles, m. p. 190—192°, from benzene–acetone (Found: C, 56·5; H, 3·2%).

Halogeno-N-methyl-2-nitrobenzanilides.—A solution of 4′-bromo-2-nitrobenzanilide (30 g.) in acetone (200 c.c.) and 20% aqueous sodium hydroxide (200 c.c.) was boiled under reflux with stirring, and methyl sulphate (60 c.c.) was slowly added. When cold, the mixture was diluted with ice-water, and an oil separated which solidified. Recrystallisation from alcohol gave *4′-bromo-N-methyl-2-nitrobenzanilide* (29 g.) in needles, m. p. 118—119° (Found: C, 49·9; H, 3·5. $C_{14}H_{11}O_3N_2Br$ requires C, 50·2; H, 3·3%). In similar manner 4′-chloro-2-nitrobenzanilide (20 g.) gave *4′-chloro-N-methyl-2-nitrobenzanilide* (18 g.) in prisms, m. p. 112—113°, from alcohol (Found: C, 58·1; H, 3·9. $C_{14}H_{11}O_3N_2Cl$ requires C, 57·9; H, 3·8%), and 2′-chloro-2-nitrobenzanilide (10 g.) gave *2′-chloro-N-methyl-2-nitrobenzanilide* (9 g.) in prisms, m. p. 127—128°, from alcohol (Found: C, 58·2; H, 4·2%). The latter compound was also prepared by the *o*-nitrobenzoylation of *o*-chloro-*N*-methylaniline. To 2-chlorotoluene-*p*-sulphonanilide (m. p.

* The copper powder used in this and subsequent experiments was prepared from zinc dust and aqueous copper sulphate.

104—105°; 18·4 g.) in warm 16% aqueous sodium hydroxide, methyl sulphate (10 c.c.) was slowly added. The oil which separated solidified and when crystallised from benzene–light petroleum (b. p. 80—100°) gave *2-chloro-N-methyltoluene-p-sulphonanilide* (17 g.) in needles, m. p. 97—98° (Found: C, 56·8; H, 5·1. $C_{14}H_{14}O_2NSCl$ requires C, 57·1; H, 4·7%). Hydrolysis of the latter (15 g.) with 60% sulphuric acid (100 c.c.) at 110° for 1 hour, followed by pouring into an excess of ice-cold aqueous ammonia, gave *o*-chloro-*N*-methylaniline (5 g.), which was extracted with ether and collected at 126°/20 mm. *o*-Nitrobenzoyl chloride (from 6 g. of acid) in ether was added to the base (5 g.) in pyridine (30 c.c.), and after removal of the ether the mixture was boiled for 5 minutes. When cold the whole was added to water, 2′-chloro-*N*-methyl-2-nitrobenzanilide (8·1 g.) separating, which crystallised from alcohol in prisms, m. p. 128°, identical with the sample prepared above.

Decomposition of the Diazonium Fluoroborates prepared from 2-Amino-4′-bromo- and 2-Amino-4′-chloro-N-methylbenzanilide.—A suspension of iron filings (30 g.) in 5% aqueous acetic acid (50 c.c.) was heated on a steam-bath with stirring until no more hydrogen was evolved, then 4′-bromo-*N*-methyl-2-nitrobenzanilide (12 g.) was added slowly. After 1 hour on the steam-bath the mixture was neutralised with aqueous sodium carbonate, and charcoal was added to assist filtration. Both filtrate and residue were repeatedly extracted with hot benzene. The combined extracts on evaporation gave the base as an oil (8·4 g.), which charred on attempted distillation under reduced pressure. It was therefore diazotised in concentrated sulphuric acid (40 c.c.) and water (100 c.c.) with sodium nitrite (3 g.) in water (15 c.c.). A solution of sodium fluoroborate (15 g.) in water (30 c.c.) was added slowly with stirring to the filtered diazonium salt solution cooled to 0°. The diazonium fluoroborate separated as an orange solid. Crystallisation from acetone–light petroleum (b. p. 40—60°) gave *4′-bromo-N-methylbenzanilide-2-diazonium fluoroborate* (7 g.) in yellow-orange prisms, m. p. 112° (decomp.) (Found: C, 41·3; H, 2·5. $C_{14}H_{11}ON_3Br,BF_4$ requires C, 41·6; H, 2·7%). In similar manner 4′-chloro-*N*-methyl-2-nitrobenzanilide (12 g.) gave the base (9·1 g.) from which *4′-chloro-N-methylbenzanilide-2-diazonium fluoroborate* (10 g.) was obtained in yellow-orange prisms, m. p. 107° (decomp.) (Found: C, 46·8; H, 3·4. $C_{14}H_{11}ON_3Cl,BF_4$ requires C, 46·8; H, 3·1%). The 4′-bromo-*N*-methylbenzanilide-2-diazonium fluoroborate (6·4 g.) in acetone suspension was decomposed by the addition of copper powder as described above for the benzotoluidide-diazonium fluoroborates. Concentration of the alkali-washed and dried chloroform solution gave an orange solid (4·2 g.), which was dissolved in benzene–light petroleum (b. p. 60—80°) (4 : 1) and adsorbed on an alumina column (30 × 2 cm.). Elution with the same mixed solvent (800 c.c.) gave *3-bromo-10-methylphenanthridone* (1·5 g.), which crystallised from benzene-light petroleum (b. p. 80—100°) in needles, m. p. 188—189° (Found: C, 58·6; H, 3·6. $C_{14}H_{10}ONBr$ requires C, 58·3; H, 3·6%). Further elution with the mixed solvent and then with benzene (800 c.c.) gave a second *substance* (0·4 g.) in buff plates, m. p. 235°, from aqueous acetic acid (Found: C, 76·3; H, 5·2; N, 6·6%). Subsequent elution with various solvents gave only gums. Acidification of the original alkaline washings gave only a trace of brown gum. In a similar manner 4-′chloro-*N*-methylbenzanilide-2-diazonium fluoroborate (9·4 g.) gave *3-chloro-10-methylphenanthridone* (2·8 g.), which crystallised from methanol in needles, m. p. 192° (Found: C, 68·8; H, 4·2. $C_{14}H_{10}ONCl$ requires C, 69·0; H, 4·2%), and a second *substance* (0·7 g.) in plates, m. p. 208—210°, from aqueous acetic acid (Found: C, 73·5; H, 5·6; N, 6·3%). Again, acidification of the alkaline washings gave only a trace of a dark gum.

2-Amino-2′-chloro-N-methylbenzanilide.—(*a*) Reduction of the nitro-compound (7 g.) with iron and acetic acid as described above for the *p*-halogeno-compounds gave, on evaporation of the benzene extracts, a solid which on crystallisation from benzene–light petroleum (b. p. 80—100°) afforded *2-amino-2′-chloro-N-methylbenzanilide* (4·1 g.) in needles, m. p. 109—110·5° (Found: C, 64·9; H, 5·3. $C_{14}H_{13}ON_2Cl$ requires C, 64·5; H, 5·0%). (*b*) A solution of the nitro-compound (5 g.) in ethanol (100 c.c.) was shaken with Raney nickel (5 g.) and hydrogen at atmospheric pressure for 1½ hours. When 1150 c.c. of hydrogen had been absorbed the suspension was filtered and the filtrate concentrated under reduced pressure. Crystallisation of the solid residue from benzene–light petroleum (b. p. 80—100°) gave 2-amino-2′-chloro-*N*-methylbenzanilide (3·3 g.) in needles, m. p. 113—115° undepressed on admixture with the product prepared by method (*a*) (Found: C, 64·0; H, 5·3%).

2′-Chloro-N-methylbenzanilide-2-diazonium Fluoroborate.—The amine (4 g.) in concentrated sulphuric acid (20 c.c.) and water (40 c.c.) was diazotised with sodium nitrite (1·5 g.) in water (10 c.c.) and to the filtered solution at 0° a solution of sodium fluoroborate (7 g.) in water (10 c.c.) was added slowly with stirring. Crystallisation of the separated solid from acetone–light petroleum (b. p. 40—60°) gave *2′-chloro-N-methylbenzanilide-2-diazonium fluoroborate*

(4·2 g.) in pale yellow prisms, m. p. 119° (decomp.) (Found: C, 46·9; H, 3·3. $C_{14}H_{11}ON_3Cl,BF_4$ requires C, 46·8; H, 3·1%).

Decomposition of the Diazonium Sulphate prepared from 2-Amino-2'-chloro-N-methylbenzanilide.—The amine (3 g.) was diazotised as described above and the filtered diazonium sulphate solution was heated for 1 hour on a boiling-water bath. When cold the mixture was extracted with chloroform. Evaporation of the alkali-washed chloroform extract gave a dark gum (2 g.), but adsorption from benzene solution on an alumina column and subsequent elution with the same solvent gave only a waxy *substance* (0·7 g.), m. p. 70—75°, from methanol (Found: C, 67·4; H, 4·1; Cl, 15·2%), a red oil, and a pale yellow *substance* (0·3 g.), m. p. 246—250°, from methanol (Found: C, 60·9; H, 4·0; Cl, 13·5%). Acidification of the alkaline extract gave a dark solid (1·2 g.), which was adsorbed from benzene solution on a silica-gel column (10 × 1 cm.). Elution with the same solvent gave a white solid, which crystallised from aqueous methanol as needles of *2'-chloro-2-hydroxy-N-methylbenzanilide* (0·2 g.), m. p. 92° (Found: C, 64·4; H, 4·7. $C_{14}H_{12}O_2NCl$ requires C, 64·3; H, 4·6%).

Carbomethoxy-N-methylphenanthridone.

4-Carbomethoxy-N-methyl-2-nitrobenzanilide.—Methyl 4-carboxy-3-nitrobenzoate (15 g.), kindly provided by Dr. B. H. Chase, was boiled under reflux for 2 hours with an excess of thionyl chloride (50 c.c.). The crude acid chloride, obtained on removal of the excess of thionyl chloride, in ether, was added slowly to a solution of methylaniline (30 c.c.) in pyridine (50 c.c.). The ether was evaporated and the pyridine solution was boiled for 5 minutes, cooled, and added to cold dilute hydrochloric acid. The brown oil solidified. Recrystallisation from aqueous alcohol (charcoal) or benzene–light petroleum (b. p. 80—100°) gave *4-carbomethoxy-N-methyl-2-nitrobenzanilide* (12·6 g.) in needles, m. p. 124—125°, which became coloured on exposure to light (Found: C, 61·2; H, 4·4. $C_{16}H_{14}O_5N_2$ requires C, 61·3; H, 4·5%).

2-Amino-4-carbomethoxy-N-methylbenzanilide.—The nitro-compound (12 g.) was added slowly to a suspension of iron filings (50 g.) in 5% aqueous acetic acid (100 c.c.) which had been heated on a steam-bath with stirring until no more hydrogen was evolved. After 1 hour's further stirring on the steam-bath the solution was neutralised with aqueous sodium carbonate and filtered with added charcoal. Both filtrate and residue were well extracted with hot benzene, and concentration of the combined extracts gave *2-amino-4-carbomethoxy-N-methylbenzanilide* (9·1 g.) in prisms, m. p. 138° (Found: C, 67·8; H, 5·8. $C_{16}H_{16}O_3N_2$ requires C, 67·6; H, 5·6%).

Decomposition of the Diazonium Sulphate prepared from 2-Amino-4-carbomethoxy-N-methylbenzanilide.—The amine (3 g.) was diazotised in sulphuric acid (5 c.c.) and water (100 c.c.) by the addition of sodium nitrite (1 g.) in water (10 c.c.). The filtered solution was decomposed and the products worked up as described above for the benzotoluidide-diazonium sulphates. Evaporation of the alkali-washed chloroform solution left a brown solid (1·82 g.), which was adsorbed on an alumina column (20 × 2 cm.) from benzene–light petroleum (b. p. 60—80°) (4 : 1). Elution with benzene (800 c.c.) gave a white solid, which crystallised from benzene–light petroleum (b. p. 80—100°) in needles of *6-carbomethoxy-10-methylphenanthridone* (1 g.), m. p. 165° (Found: C, 71·9; H, 5·1. $C_{16}H_{13}O_3N$ requires C, 71·9; H, 4·9%). Further elution with benzene–ether (3 : 1) (450 c.c.) gave a second *substance* in pale yellow needles, m p. 151—152°, from benzene–light petroleum (b. p. 80—100°) (Found: C, 67·1; H, 5·0%; *M*, 285). Acidification and extraction of the alkaline washings gave a brown tar (1·73 g.), which was adsorbed from benzene on a column of silica gel (10 × 2 cm.). Elution with the same solvent (350 c.c.) gave *4-carbomethoxy-2-hydroxy-N-methylbenzanilide* (0·46 g.) in needles, m. p. 181° (Found: C, 67·4; H, 5·0. $C_{16}H_{15}O_4N$ requires C, 67·4; H, 5·3%).

Decomposition of the Diazonium Fluoroborate prepared from 2-Amino-4-carbomethoxy-N-methylbenzanilide.—The diazonium fluoroborate, prepared from the amine (3 g.), was decomposed and the products were worked up as in the examples given above. Evaporation of the alkali-washed chloroform extract left a pale brown solid (2·85 g.), which was dissolved in benzene–light petroleum (b. p. 60—80°) (4 : 1) and purified by adsorption on alumina. In this manner 6-carbomethoxy-10-methylphenanthridone (1·1 g.) was again obtained in needles, m. p. 164—165°. In addition to brown gums, a small quantity of a second compound, m. p. 240—245°, was obtained on further elution with benzene. Acidification and extraction of the alkaline washings gave only a minute quantity of a red tar.

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776. *The Chemistry of Western Australian Plants. Part VI.* The Occurrence of Betulic, Oleanolic, and Ursolic Acids.*

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Ursolic and oleanolic acids have been identified in *Anthocercis littorea*, *Anthocercis odgersii*, and the coastal form of *Alyxia buxifolia*. Oleanolic acid has also been obtained from *Petalostigma sericea*. Betulic acid has been obtained from the inland form of *Alyxia buxifolia*, from *Nuytsia floribunda* and from six *Melaleuca* species. " Melaleucin " is probably betulic acid.

Although fairly widely distributed in the plant kingdom ursolic acid has been reported only from the Solanaceæ in the Australian genera *Duboisia* (Trautner and Neufeld, *Aust. Chem. Inst. J. and Proc.*, 1947, **14**, 17; Bottomley and White, *Australian J. Sci. Res.*, 1951, *A*, **4**, 107) and *Anthotroche* (Bottomley and White, *Australian J. Sci. Res.*, 1950, *A*, **3**, 516). It has now been found, together with oleanolic acid, in two further solanaceous plants, *Anthocercis littorea* Labill. and *Anthocercis odgersii* F. Muell. A third member of the same genus, *Anthocercis intricata* F. Muell., also contains a mixture of triterpene acids which is probably similar, although the acids have not been separated.

In the Apocynaceæ, *Petalogstigma sericea* (R.Br.) C. A. Gardn. and *Alyxia buxifolia* R.Br. have been examined. The former contains oleanolic acid, while the coastal form of the latter, like the *Anthocercis* spp., contains both oleanolic and ursolic acids. However, *Alyxia buxifolia* specimens collected from low-rainfall areas away from the coast contain betulic acid.

Betulic acid has also been isolated from *Nuytsia floribunda* (Labill.) R.Br. (Loranthaceæ), the Western Australian Christmas tree, where it is accompanied by a small amount of betulin, and from the barks of six Melaleuca species, *M. rhaphiophylla* Schau., *M. cuticularis* Labill., *M. viminea* Lindl., *M. leucadendron* L., *M. parviflora* Lindl., and *M. pubescens* Schau. The first five of these belong to the group popularly known as " paper-barks " and crystalline triterpene acid can be seen in places between the thin papery layers of the bark.

The substance isolated from the bark of *Melaleuca leucadendron* and named " melaleucin " by Isii and Osima (*J. Agric. Chem. Soc., Japan*, 1939, **15**, 839) is probably impure betulic acid. The formula proposed by them, $C_{28}H_{45}O_3$, contravenes valency requirements and requires carbon and hydrogen values (C, 78·2; H, 10·6%) reasonably close to those for $C_{30}H_{48}O_3$ (C, 78·9; H, 10·6%), while the m. p.s reported for the compound (304°) and its acetate (280°) are not far removed from those of betulic acid and its acetate, especially if they were uncorrected.

Experimental

M. p.s are corrected. Unless otherwise indicated they were determined in open tubes. Analyses are by Drs. Weiler and Strauss, Oxford, and Dr. Zimmermann, Melbourne. The identity of all the compounds prepared was checked by mixed m. p. with authentic specimens. No depressions were observed. Rotations are in chloroform solution unless otherwise indicated.

Alyxia buxifolia.—(*a*) Leaves (4·5 kg.) collected at Kalgoorlie in October, 1943, and near Morawa in August, 1945, were powdered and extracted with alcohol, and the extract (350 g.) extracted with ether. Sodium salts (43·5 g.) were precipitated by treatment of the ethereal solution with N-sodium hydroxide, and were purified by treatment of a solution in 50% alcohol with charcoal, followed by acidification. The precipitated acid was dissolved in a 5% solution of potassium hydroxide in 50% alcohol, the solution treated with charcoal, and then with acid, and the solid (35 g.) crystallised from methanol (7 times) and then from ethanol (3 times); it had m. p. 308—309°. When it was acetylated, betulic acid acetate, m. p. 289—290°, was obtained, and this was hydrolysed to betulic acid, m. p. 310—311° [methyl betulate, m. p. 222—223° (Found: C, 79·05; H, 10·75. Calc. for $C_{31}H_{50}O_3$: C, 79·1; H, 10·7%)].

(*b*) Leaves (1 kg.), collected at Point Peron in February, 1951, were extracted with ether,

* Part V, Bottomley and White, *Australian J. Sci. Res.*, 1951, *A*, **4**, 112.

and the insoluble sodium salts (45 g.) precipitated from this extract, dissolved in methanol (charcoal), and acidified. The crude acid was dissolved in boiling methanol; on cooling, solid (*A*) (8 g.) separated. A solid (*B*) (22 g.) was obtained on concentration of the filtrate.

On crystallisation of (*A*) from ethanol (charcoal), ursolic acid (0·8 g.), m. p. 286—288°, $[\alpha]_D^{16}$ +69° (*c*, 0·68 in 1 : 1-methanol–chloroform), was obtained (acetate, m. p. 289—290°; methyl ester, m. p. 170—171°; and methyl ester acetate, m. p. 245—246°).

Crystallisation of (*B*) from ethanol and removal of a low-melting first crop gave oleanolic acid (0·8 g.), m. p. 309—312°, $[\alpha]_D^{15}$ +80° (*c*, 0·93), after six crystallisations from ethanol (acetate, m. p. 267—268°; methyl ester, m. p. 201°; and methyl ester acetate, m. p. 222°).

Anthocercis littorea.—Powdered leaves and stems, collected at City Beach, near Perth, were extracted with alcohol, the residue, obtained by removal of the alcohol, was washed with 1% hydrochloric acid, and the insoluble material (42 g.) dissolved in a 2% solution of sodium hydroxide in 70% aqueous methanol and warmed (charcoal) for 30 minutes. Acidification of the filtered solution, gave the crude acid (23·5 g.), from which some impurities were removed by light petroleum. A solution of the acid in methanol (670 ml.) was treated with charcoal and then evaporated (about 100 ml. at a time), yielding six fractions, which were fractionated from methanol by a triangular scheme. The less soluble fractions and the most soluble fractions, after repeated crystallisation from ethanol, yielded ursolic acid (1·5 g.), m. p. 286—287° (vac.), $[\alpha]_D^{15}$ +70° (*c*, 1·02 in 1 : 1-methanol–chloroform) [methyl ester, m. p. 171°; acetate, m. p. 292°; and methyl ester acetate, m. p. 246—247° (vac.)]. From the fourth fraction oleanolic acid (0·5 g.), m. p. 311—312° (vac.), $[\alpha]_D^{15}$ +79° (*c*, 0·63), was obtained after two crystallisations from methanol and three from ethanol [methyl ester, m. p. 201°; acetate m. p. 268° (vac.); and methyl ester acetate, m. p. 222°].

Anthocercis odgersii.—Leaves and stems (420 g.), collected at Chandler, near Merredin, were powdered and extracted with alcohol, and the extract (42 g.) was worked up as described for *A. littorea*. Ursolic acid (10 g.), m. p. 286—287°, was obtained [methyl ester, m. p. 169—170°; acetate, m. p. 287—289°; and methyl ester acetate, m. p. 242—243°] together with a small amount of oleanolic acid, m. p. 311—312° (vac.) [methyl ester, m. p. 201°].

Anthocercis intricata.—This plant, collected in the Geraldton district, yielded a similar mixture of triterpene acids, but pure components have not been separated.

Melaleuca *spp.*—The bark (400 g.) of *Melaleuca rhaphiophylla*, collected at South Perth, was powdered and extracted with ether. The extract was treated with sodium hydroxide solution, and the precipitated sodium salts collected, dried, and dissolved in methanol (charcoal), and the solution acidified with hydrogen chloride. The crude acid, crystallised from methanol and then from ethanol, had m. p. 314—315°, $[\alpha]_D^{25}$ +8·4° (*c*, 1·36 in pyridine) (Found: C, 78·9; H, 10·8%; equiv., 446. Calc. for $C_{30}H_{48}O_3$: C, 78·9; H, 10·6%; equiv., 456·7). It formed betulic acid acetate, m. p. 293—294° (Found: C, 77·3; H, 10·0. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1%), and methyl betulate, m. p. 223—224° (Found: C, 79·0; H, 10·5. Calc. for $C_{31}H_{50}O_3$: C, 79·1; H, 10·7%). *M. cuticularis*, *M. leucadendron*, *M. parviflora*, *M. pubescens*, and *M. viminea* barks also yielded betulic acid (identified as the acetate and methyl ester) when extracted as described above.

Nuytsia floribunda.—Leaves and stems (2 kg.), collected from the University grounds, were powdered and extracted with alcohol. The alcohol was removed, the residue was extracted with ether, and the sodium salts (55 g.) were precipitated. A solution in 50% ethanol (charcoal) was acidified, and the crude acid (34 g.) purified by crystallisation from ethanol and methanol, whereby needles of betulic acid, m. p. 320—321°, $[\alpha]_D^{15}$ +12° (*c*, 0·94 in pyridine), were obtained [acetate, m. p. 295°, $[\alpha]_D^{15}$ +24° (*c*, 1·56) (Found: C, 77·3; H, 10·0%); methyl ester, m. p. 222°, $[\alpha]_D^{15}$ +7·2° (*c*, 1·11) (Found: C, 78·9; H, 10·8%)].

From the ethereal extracts, betulin, m. p. 256° (diacetate, m. p. 215°), separated.

Petalostigma sericea.—Husks of the fruit (720 g.) were extracted with ether, the crude sodium salts were precipitated and dissolved in methanol, and the solution was acidified with hydrogen chloride. Oleanolic acid, m. p. 309—311°, $[\alpha]_D^{16}$ +82° (*c*, 0·84), was obtained on crystallisation of the precipitate from methanol (Found: C, 78·9; H, 10·4. Calc. for $C_{30}H_{48}O_3$: C, 78·9; H, 10·6%). It was identified by conversion into the acetate, m. p. 267—268° (Found: C, 77·1; H, 10·0; Ac, 8·5. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1; Ac, 8·6%), methyl ester, m. p. 201° (Found: C, 79·4; H, 10·5. Calc. for $C_{31}H_{50}O_3$: C, 79·1; H, 10·7%), and methyl ester acetate, m. p. 222°, $[\alpha]_D^{16}$ +71° (*c*, 0·98).

Thanks are due to the Commonwealth Research Grant to Australian Universities for financial support, to Mr. C. A. Gardner, Dr. N. H. Brittan, and Mr. G. G. Smith for the collection and

identification of the plants, to Mr. W. J. Dunstan for authentic specimens of oleanolic acid and its derivatives, and to Mr. D. T. Downing and Mr. L. S. Zampatti for assistance with some of the experimental work.

UNIVERSITY OF WESTERN AUSTRALIA, NEDLANDS. [*Received, June 3rd,* 1952.]

777. *Antituberculous Compounds. Part X.* Some Reactions of Quaternary Compounds Derived from* NN*-Disubstituted Thioamides.*

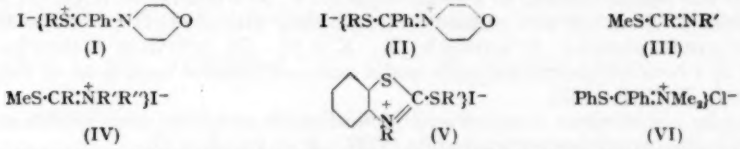
By D. A. PEAK and F. STANSFIELD.

Whereas semicarbazide reacts with the quaternary "methiodide" (II: R = Me) of thiobenzomorpholide to give 1-α-methylthiobenzylidenesemicarbazide (VII; R = Ph, X = O) (Chabrier and Renard, *Compt. rend.*, 1950, **230**, 1673; *Bull. Soc. chim.*, 1951, **18**, 348), thiosemicarbazide yields by cyclisation 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (IX). Under alkaline conditions semicarbazide condenses with (II; R = Me) with the elimination of methanethiol instead of morpholine hydriodide to give 1-α-morpholinobenzylidenesemicarbazide (VIII; R = Ph, X = O). Thiosemicarbazide reacts analogously and the reaction is general for quaternary derivatives of other thioamides, both open-chain and cyclic, and fully substituted thiuronium salts. The compounds so obtained have low antituberculous activity.

The course of the reaction between (II; R = Me) and ammonia to give benzamidine has been investigated. Aniline reacts with (II; R = Me) to give the *NNN'*-trisubstituted benzamidine salt (XX) whilst morpholine gives the quaternary amidinium salt (XXI; R = Ph).

The quaternised thioacylmorpholides are readily thiohydrolysed by hydrogen sulphide, and the reaction constitutes a convenient source of dithiocarboxylic esters.

CHABRIER and RENARD (*Compt. rend.*, 1950, **230**, 1673) have described the reaction of methyl and ethyl iodide with thiobenzomorpholide giving quaternary derivatives to which they assigned the structure (I; R = Me or Et). Böttcher and Bauer (*Annalen*, 1950, **568**, 218) obtained similar compounds by the action of methyl iodide on *S*-methyl*iso*thioamides of type (III) and represented these by the structure (IV; R'' = Me). Analogous cyclic quaternary derivatives, *e.g.*, 2-alkylthiobenzothiazole alkiodides (V), have also



(I) (II) (III)

(IV) (V) (VI)

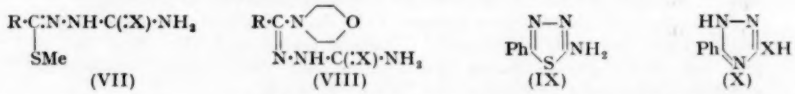
generally been formulated as ammonium rather than sulphonium derivatives. Fry and Kendall (*J.*, 1951, 1716) have recently shown that it is not even necessary to postulate the intermediate existence of the sulphonium form as suggested by Davies and Sexton (*J.*, 1942, 304) and Mann and Watson (*J. Org. Chem.*, 1948, **13**, 502) to explain the formation of mixtures of quaternary salts when R and R' are different alkyl groups.

We are indebted to Dr. J. D. S. Goulden for the examination of the infra-red absorption spectra of the Chabrier–Renard compounds. The main features are the absence of a band in the 1300—1400-cm.$^{-1}$ region, where a thiono-group (C:S) normally absorbs, and a strong band at 1580 cm.$^{-1}$. This is somewhat lower than the frequency usually associated with the C:N$^+$ group (Randall, Fowler, Fuson, and Dangl, "Infrared Determination of Organic Structures," Van Nostrand Co, Inc., New York, 1949, p. 5) probably owing to the effect of the substituent methylthio-group. If a resonance hybrid state exists between these two forms, therefore, the contribution of the sulphonium form must be small and the compounds are more accurately represented by (II) than by (I). The ready hydrolysis

* Part IX, *J.*, 1951, 3292.

of the compounds to alkyl thiolbenzoates is also in conformity with the absence of resonance stabilisation. Raison (*J.*, **1949**, **3319**) came to similar conclusions regarding the structure of his hypothetical intermediate (VI) from the condensation of benzodimethylamide and thiophenol in the presence of phosphoryl chloride.

Chabrier and Renard (*loc. cit.*) observed that (II; R = Me) condensed with semicarbazide hydrochloride in aqueous ethanol to give the compound (VII; R = Ph, X = O). This reaction appeared of considerable interest since an analogous condensation with thiosemicarbazide might lead to 1-α-alkylthiobenzylidenethiosemicarbazides (VII; R = aryl, X = S) which, because of their close relationship to thiosemicarbazones such as *p*-acetamidobenzaldehyde thiosemicarbazone ("Thiacetazone"), might possess chemotherapeutic activity against *Mycobacterium tuberculosis*. Compound (II; R = Me) was found to condense with thiosemicarbazide under acid or neutral conditions with, presumably, the intermediate formation of (VII; R = Ph, X = S) which, however, was too unstable for isolation since it readily cyclised to 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (IX) with the loss of methanethiol. This spontaneous cyclisation is in contrast to the behaviour of the oxygen analogue (VII; R = Ph, X = O) which does not cyclise. The latter is unaffected by ethanolic alkali but with aqueous ethanolic hydrochloric acid it undergoes rapid fission to methyl thiolbenzoate and semicarbazide. The *p*-ethanesulphonyl derivative (VII; R = *p*-Et·SO_2·C_6H_4, X = O) is similarly cleaved. On pyrolysis at 210° (VII; R = Ph, X = O) cyclises to 3-hydroxy-5-phenyl-1 : 2 : 4-triazole (X; X = O).



(VII) (VIII) (IX) (X)

The compound (VII; R = Ph, X = O) showed appreciable antituberculous activity *in vitro* but an attempt to exploit this by the introduction of *p*-substituents which exert a favourable influence in the thiosemicarbazone type of compound, *e.g.*, methoxy, acetamido, and ethanesulphonyl, afforded compounds devoid of activity.

Under alkaline conditions, *e.g.*, in aqueous potassium hydrogen carbonate or in pyridine, preferably in the presence of a strong base such as di- or tri-ethylamine, the condensation of (II; R = Me) with thiosemicarbazide took a different course, the methylthio-group being eliminated instead of the morpholino-group, with the formation of 1-α-morpholinobenzylidenethiosemicarbazide (VIII; R = Ph, X = S). This compound was soluble in dilute acids but was rapidly cyclised to 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (IX). It was much more stable to alkali but was cyclised by long boiling with alcoholic potassium hydroxide to 3-mercapto-5-phenyl-1 : 2 : 4-triazole (X; X = S). Its behaviour is therefore similar to that of 1-benzoylthiosemicarbazide under acid and alkaline conditions of dehydration (Hoggarth, *J.*, **1949**, **1163**).

A similar condensation occurred with semicarbazide under the same conditions, to give 1-α-morpholinobenzylidenesemicarbazide (VIII; R = Ph, X = O).

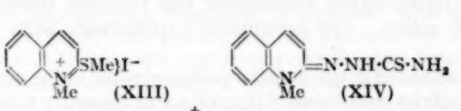
This reaction was found to be quite general. A number of *NN*-disubstituted thioamides (XI) were prepared by standard procedures and converted into the methiodides (IV) in which R was variously aryl, alkyl, or aralkyl and R′ and R″ were either aryl or

(XI) R·CS·NR′R″ R·C(NR′R″):N·NH·CS·NH_2 (XII)

alkyl or jointly the residue of a heterocycle such as morpholine or piperidine. These readily afforded the thiosemicarbazono-derivatives (XII), none of which, however, exhibited appreciable activity *in vitro*. 1-α-Morpholinobenzylidenesemicarbazide (VIII; R = Ph, X = O) showed activity *in vitro* comparable to that of "Thiacetazone" but it had no action on experimental tuberculosis in mice.

The reaction was found to be equally applicable to quaternary derivatives of cyclic thioamides. Thus, 1-methyl-2-methylthioquinolinium iodide (XIII) with thiosemicarbazide readily gave 1 : 2-dihydro-1-methyl-2-thiosemicarbazonoquinoline (XIV) and a "vinylogue," 1 : 4-dihydro-1 : 2-diphenyl-4-thiosemicarbazonoquinoline (XV), was similarly obtained from 4-methylthio-1 : 2-diphenylquinolinium iodide. Analogous thiosemi-

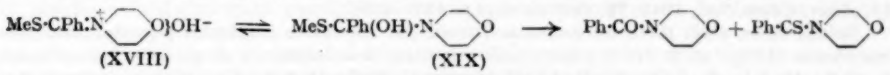
carbazono-derivatives of other heterocycles such as pyridine, *iso*quinoline, benzothiazole, and pyrimidine were obtained from the appropriate quaternised methylthio-heterocyclic compounds. The reaction also proceeded with fully substituted thiuronium salts. Thus *SN*-dimethyl-*NN'*-diphenyl*iso*thiourea was quaternised with methyl iodide and the product condensed with thiosemicarbazide, to give *NN'*-dimethyl-*NN'*-diphenyl-*N''*-thioureidoguanidine (XVII). The intermediate quaternary derivative must therefore



(XVI) PhMeN·C(SMe):$\overset{+}{N}$MePh}I⁻ PhMeN·C(·NMePh):N·NH·CS·NH₂ (XVII)

have the structure (XVI), in accordance with the general rule that the doubly-linked nitrogen atom of an amidine group is preferentially attacked by a quaternising or alkylating agent (Pyman, *J.*, 1923, **123**, 3362).

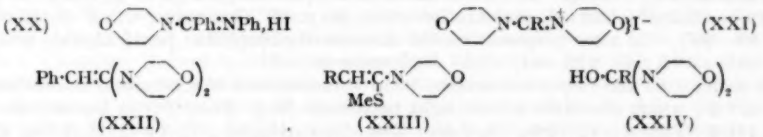
Chabrier and Renard observed that a solution of (II; R = Me) in aqueous ammonia soon deposited an oil which later solidified and finally redissolved, the end products being benzamidine and morpholine hydriodide. Examination of this solid has shown that its properties are consistent with its formulation as a *pseudo*-base (XIX), corresponding to the hypothetical quaternary hydroxide (XVIII). It is too unstable to be satisfactorily purified for analysis. It is an almost neutral substance but is reconverted by hydrogen iodide into the original compound (II; R = Me). When boiled with aqueous ethanol it



(XVIII) (XIX)

gives a mixture of benzo- and thiobenzo-morpholide which could be formed by loss of either methanethiol or methanol from (XIX). It is an intermediate and not a side-product in the formation of benzamidine since it affords benzamidine when dissolved in aqueous ammonia, although some thiobenzomorpholide is simultaneously formed.

Under similar conditions, Chabrier and Renard showed that the primary amine, methylamine, gave *NN'*-dimethylbenzamidine while the secondary amine, diethylamine, gave mainly thiobenzomorpholide with some benzodiethylamide. Under anhydrous conditions the reaction with primary and secondary amines proceeds differently. Thus, (II; R = Me) with aniline afforded the expected *N*-phenylbenzimidoylmorpholide hydriodide (XX). With morpholine, the quaternary amidinium compound (XXI;



(XXII) (XXIII) (XXIV)

R = Ph) was formed. The structure of this compound is unambiguous but it is possible to formulate the analogous phenylacetamidinium derivative, similarly obtained although not in an analytically pure state, either as (XXI; R = Ph·CH_2) or as the hydriodide of (XXII). A similar doubt applies to the quaternary methiodides of thioaceto- and phenylthioacetomorpholide, which might exist as the hydriodides of (XXIII; R = H and Ph respectively). This is unlikely because of the great similarity of the infra-red spectra to that of (II). We have, however, confirmed Rogers' observation (*J.*, 1950, 3350) that, in the presence of excess of aqueous morpholine, (XXI; R = Ph·CH_2) loses the elements of hydrogen iodide and gives a compound which can be formulated only as (XXII). On the other hand, (XXI; R = Ph) is rapidly converted into benzomorpholide and morpholine by one equivalent of alkali, presumably *via* the unstable *pseudo*-base (XXIV; R = Ph) which cannot attain a stable state by the elimination of water as in the case of (XXIV; R = Ph·CH_2).

The ready hydrolysis of (II; R = Me) to methyl thiolbenzoate suggested that com-

pounds of this type might also react with hydrogen sulphide to give dithiocarboxylic esters. This proved to be the case and (II; R = Me) reacted readily with hydrogen sulphide in pyridine or ethanol to give methyl dithiobenzoate (64%). 4-(1-Methylthio-2-phenylethylidene)morpholinium iodide similarly gave methyl phenyldithioacetate (44%), and 4-1′-methylthioethylidenemorpholinium iodide gave methyl dithioacetate (77%), obtained as a methanol azeotrope and estimated by conversion into thioacetobenzylamide. Because of the ready availability of *NN*-disubstituted thioamides the reaction offers a very convenient route to dithiocarboxylic esters. The intermediate quaternary salts need not be isolated.

During this work discrepancies were noted in the melting-points of some of the compounds compared with those recorded by Chabrier and Renard (*loc. cit.*) and these are noted in the Experimental section.

Experimental

All m. p.s uncorrected.

Preparation of Thioamides and iso*Thioamides.—Method A* (Willgerodt–Kindler reaction). Benzaldehyde (42·5 g.), morpholine (52·0 g., 1·5 mols.), and sulphur (19·2 g., 1·5 atoms) were heated together under reflux on the steam-bath. An exothermic reaction occurred and the mixture boiled. After 3 hours' heating, the resulting dark brown oil (which sometimes solidified) was dissolved in boiling ethanol (800 c.c.), and the hot solution was filtered from a small insoluble residue. The filtrate, on cooling, deposited thiobenzomorpholide as golden-yellow needles (73·5 g., 0·89 mol.), m. p. 135—136°. It still contained a small amount of sulphur, which could be removed, if desired, by shaking it with concentrated sodium sulphide solution. McMillan (*J. Amer. Chem. Soc.*, 1948, **70**, 869) gives m.p. 137—138°.

In the same way, there were obtained from the respective aldehydes p-*methoxythiobenzomorpholide* (83%; m. p. 107°), golden-yellow needles (from ethanol), m. p. 109—110° (Found: C, 61·3; H, 6·4; N, 5·55. $C_{12}H_{15}O_2NS$ requires C, 60·8; H, 6·3; N, 5·9%), p-*acetamidothiobenzomorpholide* (94%; m. p. 211—215°), lemon yellow elongated plates (from ethanol), m. p. 214—216° (Found: N, 10·9. $C_{13}H_{16}O_2N_2S$ requires N, 10·6%), p-*ethanesulphonylthiobenzomorpholide* (88%), slightly yellow plates (from ethanol), m. p. 186° (Found: C, 52·65; H, 5·7. $C_{13}H_{17}O_3NS_2$ requires C, 52·2; H, 5·7%), and thiobenzopiperidide (impure product obtained as an oil) (Russell, *J.*, 1910, **97**, 955, gives m. p. 65—66°).

Method B. Acetomorpholide (60·0 g.) in carbon disulphide (80 c.c.) was shaken with phosphorus pentasulphide (103·3 g., 1 mol.) for 2 hours. Some heat was produced and the mixture was cooled occasionally. Finally the mixture was boiled under reflux on the steam-bath for 2 hours and then cooled. Water was added to decompose the phosphorus compounds and the mixture kept overnight. The product, isolated in chloroform, was obtained as an oil which solidified on cooling. The crude thioacetomorpholide (55·5 g., 82%; m. p. 80°) crystallised from ethanol (charcoal) in colourless rods, m. p. 89° (Levesque, U.S.P. 2,489,094, gives m. p. 89—90°). In some preparations the amount of phosphorus pentasulphide was reduced to as little as 0·3 mol. with only slight diminution in yield.

Similarly, from the respective amides, there were obtained *N*-methylthiobenzanilide (44%; m. p. 101·5°) which crystallised from light petroleum (b. p. 80—100°) in lemon-yellow cubes, m. p. 101·5° (Found: C, 73·6; H, 5·35. Calc. for $C_{14}H_{13}NS$: C, 74·0; H, 5·7%) (May, *J.*, 1913, **103**, 2274, gives m. p. 90—91°), and 1-methyl-2-quinolthione (not purified, crude m. p. 90°) (Gutbier, *Ber.*, 1900, **33**, 3359, gives m. p. 118°).

Method C (cf. Klingsberg and Papa, *J. Amer. Chem. Soc.*, 1951, **73**, 4988). 2-Methyl-1-*iso*quinolone (33·9 g.) was dissolved in dry pyridine (100 c.c.) under a reflux air-condenser, and phosphorus pentasulphide (56·8 g., 1·2 mols.) was added, the heat produced being sufficient to cause ebullition. When the reaction began to subside, boiling was continued over a gauze for 2 hours. The product was then poured slowly, with stirring, into water (350 c.c.) previously heated almost to boiling, to decompose phosphorus compounds. After cooling, the product was extracted with chloroform, and the extract washed with water, dried (Na_2SO_4), and treated with charcoal. Evaporation of the solvent afforded crude 2-*methyl*-1-iso*quinolthione* (23·0 g., 62%), m. p. 90°. It crystallised from light petroleum (b. p. 80—100°) as orange-yellow needles, m. p. 110° (Found: C, 68·6; H, 5·1. $C_{10}H_9NS$ requires C, 68·6; H, 5·15%).

In the same way, but without chloroform-extraction, there were obtained NNN′N′-*tetraethyldithioterephthalamide* (by using 2·4 mols. of phosphorus pentasulphide) (96%), small, deep yellow needles (from ethanol), m. p. 202—203° (Found: N, 9·3. $C_{16}H_{24}N_2S_2$ requires N, 9·1%),

1 : 2-*diphenyl*-4-*quinolthione* (69%), orange-brown needles (from ethyl acetate), m. p. 267° (Found : C, 80·6; H, 4·9. $C_{21}H_{15}NS$ requires C, 80·5; H, 4·8%), and 9-*phenanthridthione* (68%), small, deep yellow needles (from dioxan), m. p. 273—274° (Found : C, 74·15; H, 4·3. $C_{13}H_9NS$ requires C, 73·9; H, 4·2%).

9-*Methylthiophenanthridine*.—9-Phenanthridthione (18·0 g.) was boiled under reflux, moisture being excluded, with methyl iodide (50 c.c.) and dry acetone (200 c.c.) for 4 hours. After cooling, ether (200 c.c.) was added gradually, with stirring, and the solid formed was filtered off, washed with ether, and decomposed with sodium hydroxide solution. The free base was extracted with chloroform, and the solution dried (Na_2SO_4), treated with charcoal, and filtered. The solvent was evaporated, leaving 9-*methylthiophenanthridine* (11·5 g.), m. p. 70°, which after recrystallisation from ethanol, formed orange-yellow hair crystals, m. p. 70—71° (Found : C, 75·2; H, 4·8. $C_{14}H_{11}NS$ requires C, 74·65; H, 4·9%).

1-*Methyl*-2-*pyridthione*.—This was prepared by the method of Michaelis and Hölken (*Annalen*, 1904, **331**, 248).

4 : 6-*Dimethyl*-2-*methylthiopyrimidine*.—This compound was obtained by the method of Wheeler and Jamieson (*Amer. Chem. J.*, 1904, **32**, 356).

Preparation of Quaternary Salts.

The methiodides were prepared from the corresponding *NN*-disubstituted thioamides (or *N*-monosubstituted-*S*-methyl*iso*thioamides) and a large excess of methyl iodide (usually 3 mols. or more) in boiling, dry, methanol-free acetone, under reflux with exclusion of moisture for an appropriate time. If necessary, some of the solvent was then evaporated, care being taken to avoid decomposition of the methiodide by heat, and, after cooling, ether was added with stirring to the cooled concentrate. The compound (often well crystallised) was filtered off, rapidly washed with ether, and dried at once in a vacuum-desiccator. Products so obtained were used directly for further reactions, but purification for analysis was often accomplished by dissolving them in absolute ethanol at room temperature and precipitating them in crystalline form by slow addition of ether with stirring and seeding if necessary.

The quaternary salts are soluble in water, but are slowly decomposed, even by atmospheric moisture, and all melt with decomposition (usually with liberation of methyl iodide and regeneration of the thioamide).

The following compounds were prepared in this way (from the *NN*-disubstituted thioamides except where otherwise stated), reaction times and yields being given parenthetically : 4-1′-*methylthioethylidenemorpholinium iodide* (30 minutes; 99%), colourless plates (from acetone), m. p. 131—132° (decomp.) (Found : C, 29·1; H, 4·7; N, 4·9; S, 10·6. $C_7H_{14}ONIS$ requires C, 29·3; H, 4·9; N, 4·9; S, 11·15%); 4-(1-methylthio-2-phenylethylidene)morpholinium iodide, colourless, flat needles, m. p. 158° (decomp.), from nitromethane by precipitation with benzene (Found : C, 42·6; H, 4·9. Calc. for $C_{13}H_{18}ONIS$: C, 43·0; H, 4·95%) [Rogers, *loc. cit.*, gives m. p. 172° (decomp.)]; 4-α-methylthiobenzylidenemorpholinium iodide (10 minutes; 90%), thin yellow plates, m. p. 158° (decomp.), from ethanol–ether (Found : C, 41·1; H, 4·75. Calc. for $C_{12}H_{16}ONIS$: C, 41·3; H, 4·6%) (Chabrier and Renard, *Compt. rend.*, 1949, **228**, 850, give m. p. 138°; Chabrier, Renard, and Smarzewska, *Bull. Soc. chim.*, 1950, **17**, 1167, give m. p. 170°); 4-(4-*methoxy*-α-*methylthiobenzylidene*)*morpholinium iodide* (10 minutes; 86%), yellow hairs (from ethanol–ether), m. p. 142° (decomp.) (Found : C, 41·2; H, 4·7. $C_{13}H_{18}O_2NIS$ requires C, 41·15; H, 4·75%); 4-(4-acetamido-α-methylthiobenzylidene)morpholinium iodide (not purified; m. p. 136—138°); 4-(4-ethanesulphonyl-α-methylthiobenzylidene)morpholinium iodide (not purified); 1-α-*methylthiobenzylidenepiperidinium iodide* (1 hour; 58%) (overall yield based on benzaldehyde used in the Willgerodt reaction, the crude product from which was used), yellow plates (from ethanol–ether), m. p. 111° (decomp.) (Found : C, 44·7; H, 5·5. $C_{13}H_{18}NIS$ requires C, 44·95; H, 5·2%); *NN*-dimethyl-α-methylthiobenzylideneammonium iodide (Böttcher and Bauer, *loc. cit.*); N-*methyl*-α-*methylthiobenzylideneanilinium iodide* (10 minutes; 97%), elongated yellow plates (from ethanol–ether), m. p. 148—150° (decomp.) (Found : C, 49·0; H, 4·15. $C_{15}H_{16}NIS$ requires C, 48·8; H, 4·3%); αα′-*dimethylthio*-p-*xylylidenebis-diethylammonium di-iodide* (7 hours; 97%), elongaged plates (from acetone), m. p. 193—197° (decomp.) (Found : C, 36·6; H, 5·5. $C_{18}H_{30}N_2I_2S_2$ requires C, 36·5; H, 5·1%); 1-methyl-2-methylthiopyridinium iodide (Michaelis and Hölken, *loc. cit.*); 1-methyl-2-methylthioquinolinium iodide (Fischer, *Ber.*, 1902, **35**, 3677); 2-*methyl*-1-*methylthio*isoquinolinium *iodide* (2 hours; 97%), deep yellow needles (from ethanol–ether), m. p. 134° (decomp.) (Found : C, 41·5; H, 3·9. $C_{11}H_{12}NIS$ requires C, 41·65; H, 3·8%); 4-*methylthio*-1 : 2-*diphenylquinolinium iodide* (2 hours; 93%), golden-yellow plates (from ethanol–ether), m. p. 245° (decomp.) (Found :

C, 57·8; H, 4·0. $C_{22}H_{18}NIS$ requires C, 58·0; H, 3·95%); 1 : 4 : 6-*trimethyl*-2-*methylthiopyrimidinium iodide* (from 4 : 6-dimethyl-2-methylthiopyrimidine) (36 hours; 71%) (experiment by Dr. P. E. Macey), pale yellow needles (from acetone–benzene), m. p. 185° (decomp.) (Found : N, 9·2. $C_8H_{13}N_2IS$ requires N, 9·45%); and 3-methyl-2-methylthiobenzothiazolium iodide (Fry and Kendall, *loc. cit.*).

In the same way, *SN*-dimethyl-*NN'*-diphenyl*iso*thiourea (Bertram, *Ber.*, 1892, **25**, 57), with methyl iodide in boiling acetone for 24 hours, gave SNN'-*trimethyl*-NN'-*diphenylthiuronium iodide* (95%), colourless elongated plates (from ethanol–ether), m. p. 161—162° (Found : C, 48·2; H, 4·7. $C_{16}H_{19}N_2IS$ requires C, 48·2; H, 4·8%).

Thiobenzomorpholide (2·07 g.) in dry, methanol-free acetone (10 c.c.) with ethyl iodide (1·6 c.c.), under reflux for 2 hours, gave 4-α-ethylthiobenzylidenemorpholinium iodide (2·27 g.), m. p. 136°, which formed yellow plates or needles, m. p. 136—137°, from alcohol–ether (Found : C, 43·0; H, 5·0; I, 35·0. Calc. for $C_{13}H_{18}ONIS$: C, 43·0; H, 4·95; I, 35·0%) (Chabrier, Renard, and Smarzewska, *loc. cit.*, give m. p. 193°). The same compound, m. p. 136°, was obtained when thiobenzomorpholide (2·07 g.) with ethyl iodide (1·6 c.c.) in acetone (34 c.c.) was kept for 10 days at room temperature, and the product gave no depression of m. p. on admixture with the ethiodide prepared in boiling solution.

Thiosemicarbazono-derivatives.

An equimolecular mixture of thiosemicarbazide and the methiodide was dissolved or suspended in an excess of an organic base (or combination of bases) and shaken mechanically at room temperature, usually for 16 hours. Although pyridine was an excellent solvent, the reaction proceeded in some cases only very slowly unless a stronger base such as diethylamine, triethylamine, or piperidine, was present. Finally, the solvent was removed under reduced pressure (bath-temperature 40°), the residue triturated with water, and the product filtered off, washed, and dried at room temperature.

In this way there were prepared (the base or bases used and their respective volume ratio, time of reaction, and yield being indicated parenthetically in that order) : 1-1'-*morpholinoethylidenethiosemicarbazide* (diethylamine; 16 hours; 72%), colourless small cubes (from ethanol), m. p. 133° (decomp.) (Found : C, 42·05; H, 7·4; N, 27·5; S, 15·55. $C_7H_{14}ON_4S$ requires C, 41·6; H, 6·9; N, 27·7; S, 15·85%); 1-α-*morpholinobenzylidenethiosemicarbazide* (pyridine–piperidine, 7 : 1; 24 hours; 57%), colourless rods (from methyl acetate or ethanol), m. p. 141° (Found : C, 54·7; H, 6·0; N, 20·7, 21·1; S, 12·65. $C_{12}H_{16}ON_4S$ requires C, 54·55; H, 6·05; N, 21·2; S, 12·1%), also prepared from the ethiodide (piperidine; 24 hours; 84%), and from the methiodide in aqueous potassium hydrogen carbonate; 1-(4-*methoxy*-α-*morpholinobenzylidene*)*thiosemicarbazide* (diethylamine; 10 minutes; 72%), small colourless cubes (from methyl acetate), m. p. 147° (Found : C, 52·8; H, 6·1. $C_{13}H_{18}O_2N_4S$ requires C, 53·1; H, 6·1%); 1-α-*piperidinobenzylidenethiosemicarbazide* (pyridine–piperidine, 3 : 1; 16 hours; 83%), colourless cubes (from ethyl acetate), m. p. 140° (Found : N, 21·4. $C_{13}H_{18}N_4S$ requires N, 21·4%); 1-α-*dimethylaminobenzylidenethiosemicarbazide* (pyridine–triethylamine, 1 : 1; 16 hours; 71%), large colourless rhombs (from ethyl acetate), m. p. 131° (decomp.) (Found : C, 54·2; H, 6·0; N, 24·7. $C_{10}H_{14}N_4S$ requires C, 54·05; H, 6·3; N, 25·2%); 1-(α-N-*methylanilinobenzylidene*)*thiosemicarbazide* (diethylamine; 16 hours; 93%), faintly yellow flat needles (from ethanol or ethyl acetate), m. p. 152° (Found : C, 63·3; H, 5·6. $C_{15}H_{16}N_4S$ requires C, 63·4; H, 5·6%); 1 : 2-*dihydro*-1-*methyl*-2-*thiosemicarbazonopyridine* (diethylamine–pyridine, 3 : 2; 9 days; 55%), lemon-yellow cubes (from methanol), m. p. 198° (decomp.) with much darkening above 160° (Found : C, 46·1; H, 5·7. $C_7H_{10}N_4S$ requires C, 46·15; H, 5·5%); 1 : 2-*dihydro*-1-*methyl*-2-*thiosemicarbazonoquinoline* (diethylamine; 16 hours; 59%), deep yellow rods with tapering ends (from methanol), m. p. 206° (decomp.) preceded by darkening and shrinking above 180° (Found : C, 57·0; H, 5·05. $C_{11}H_{12}N_4S$ requires C, 56·9; H, 5·2%); 1 : 2-*dihydro*-2-*methyl*-1-*thiosemicarbazono*isoquinoline (pyridine–diethylamine, 5 : 1; 16 hours; 98%), greenish-yellow clusters of rods (from ethanol), m. p. 157—158° (decomp.) (Found : C, 56·3; H, 5·2%); 1 : 4-*dihydro*-1 : 2-*diphenyl*-4-*thiosemicarbazonoquinoline* (pyridine–diethylamine, 10 : 1; 4 hours; 88%), deep yellow needles (from ethanol–ethyl lactate), chars above 235° without melting (Found : C, 71·05; H, 4·8. $C_{22}H_{18}N_4S$ requires C, 71·35; H, 4·85%); 1 : 2-*dihydro*-1 : 4 : 6-*trimethyl*-2-*thiosemicarbazonopyrimidine* (pyridine–triethylamine, 10 : 1; 2 days; 82%), small orange-yellow needles (from ethanol), m. p. 202° (decomp.) (Found : C, 45·75; H, 6·3. $C_8H_{13}N_5S$ requires C, 45·5; H, 6·15%); 2 : 3-*dihydro*-3-*methyl*-2-*thiosemicarbazonobenzothiazole* (pyridine–diethylamine, 2 : 1; 54 hours; 67%), colourless rods (from ethanol), m. p. 214° (decomp.) (Found : C, 45·9; H, 4·4. $C_9H_{10}N_4S_2$ requires C, 45·4; H,

4·2%); and NN'-*dimethyl*-NN'-*diphenyl*-N''-*thioureidoguanidine* (pyridine–triethylamine, 10 : 1; 66 hours; 92%), colourless plates (from ethanol), m. p. 183° (Found: C, 61·6; H, 5·9; N, 22·6; S, 9·65. $C_{16}H_{19}N_5S$ requires C, 61·35; H, 6·1; N, 22·4; S, 10·2%).

1 : 2-*Dihydro*-1-*methyl*-2-S-*methyl*isothiosemicarbazonopyridine *Hydriodide*.—1 : 2-Dihydro-1-methyl-2-thiosemicarbazonopyridine (1·5 g.), on being heated under reflux with methyl iodide (5 c.c.) and dry acetone (20 c.c.) for 4 hours, cooled, and treated with ether, gave 1 : 2-*dihydro*-1-*methyl*-2-S-*methyl*isothiosemicarbazonopyridine *hydriodide* (2·4 g.), deep yellow clusters of plates (from ethanol), m. p. 167° (decomp.) (Found: C, 29·8; H, 3·9. $C_8H_{13}N_4IS$ requires C, 29·6; H, 4·0%). The location of the methyl group was indicated by the liberation of methanethiol with boiling 5N-sodium hydroxide.

Reaction with Acid.—1-α-Morpholinobenzylidenethiosemicarbazide (2·0 g.) was shaken with N-hydrochloric acid (25 c.c.) at room temperature. The solid quickly dissolved to a clear solution. Scratching yielded at once a white precipitate (hair crystals) which was filtered off, washed, and dried (1·0 g.). This was presumably the hydrochloride of 2-amino-5-phenyl-1 : 3 : 4-thiadiazole since with potassium hydrogen carbonate solution effervescence occurred and the free base was liberated, m. p. 225°, undepressed on admixture with an authentic specimen prepared by Hoggarth's method (*loc. cit.*).

An attempt to decompose 1 : 2-dihydro-1-methyl-2-thiosemicarbazonoquinoline by boiling it with N-hydrochloric acid for 5 minutes, led only to recovery of the starting material.

Reaction with Alkali.—1-α-Morpholinobenzylidenethiosemicarbazide (1·0 g.) was boiled under reflux for 2 hours with a solution of potassium hydroxide (1·0 g.) in alcohol (50 c.c.). After evaporation of solvent, the residue was triturated with water (25 c.c.). The undissolved solid, when filtered off, washed, and dried, proved to be unchanged starting material (0·6 g.), m. p. 141°, undepressed on admixture with the original compound. The combined filtrate and washings were acidified and the precipitated solid was filtered off, washed, and dried. This was 3-mercapto-5-phenyl-1 : 2 : 4-triazole (0·25 g.), m. p. 254°, raised by recrystallisation from aqueous ethanol to 255° and undepressed on admixture with a specimen prepared by the method of Hoggarth (*loc. cit.*).

Effect of Heat.—1-α-Morpholinobenzylidenethiosemicarbazide (4·0 g.) was heated at 180° for 1 hour. Morpholine distilled over and was removed finally *in vacuo*. The solid residue was recrystallised from aqueous ethanol (charcoal), yielding colourless crystals of 3-mercapto-5-phenyl-1 : 2 : 4-triazole (1·7 g.), m. p. and mixed m. p. 252°. It was completely soluble in dilute sodium hydroxide solution.

Semicarbazono-derivatives.

1-α-*Morpholinobenzylidenesemicarbazide*.—Semicarbazide hydrochloride (4·5 g.) was added to pyridine (30 c.c.), followed by 4-α-methylthiobenzylidenemorpholinium iodide (14·1 g., 1 mol.). The mixture was shaken for 16 hours, pyridine removed *in vacuo* (bath temperature <35°), and the residue triturated with water, filtered off, washed, and dried. The crude product (4·6 g.) was recrystallised from ethyl acetate, giving colourless needles of the *semicarbazide*, m. p. 162—163° (Found: C, 57·9; H, 6·0; N, 22·6. $C_{12}H_{16}O_2N_4$ requires C, 58·05; H, 6·45; N, 22·6%).

1-α-*Methylthiobenzylidenesemicarbazide*.—To a solution of semicarbazide hydrochloride (4·5 g.) and hydrated sodium acetate (5·5 g., 1 mol.) in water (80 c.c.) at room temperature was added 4-α-methylthiobenzylidenemorpholinium iodide (11·2 g., 0·8 mol.). After being shaken to dissolve the latter, the mixture was set aside for 16 hours. The white crystalline precipitate of the semicarbazide was filtered off, washed with water, and dried (4·2 g., 0·5 mol.; m. p. 151—153°). On recrystallisation from ethanol, it gave colourless prisms, m. p. 156—157° (Chabrier and Renard, *Bull. Soc. chim.*, 1951, **18**, 348, give m. p. 131°) (Found: C, 52·0; H, 5·25; N, 19·9. Calc. for $C_9H_{11}ON_3S$: C, 51·7; H, 5·25; N, 20·1%).

In this way there were also prepared: 1-(4-*methoxy*-α-*methylthiobenzylidene*)*semicarbazide* (52%), prisms (from ethanol), m. p. 163° (Found: C, 50·05; H, 5·25. $C_{10}H_{13}O_2N_3S$ requires C, 50·2; H, 5·45%); 1-(4-*acetamido*-α-*methylthiobenzylidene*)*semicarbazide* (59%), prisms (from ethanol), m. p. 204° (decomp.) (Found: C, 49·9; H, 5·0. $C_{11}H_{14}O_2N_4S$ requires C, 49·6; H, 5·25%); and 1-(4-*ethanesulphonyl*-α-*methylthiobenzylidene*)*semicarbazide* (20%), plates (from ethanol), m. p. 172° (Found: C, 44·0; H, 4·8. $C_{11}H_{15}O_3N_3S_2$ requires C, 43·85; H, 5·0%).

Decomposition with Acid.—A solution of 1-α-methylthiobenzylidenesemicarbazide (1·0 g.) in a mixture of concentrated hydrochloric acid (10 c.c.) and ethanol (30 c.c.), was boiled under reflux on the steam-bath for 1 hour and then evaporated to dryness at room temperature. The residue was triturated with chloroform (20 c.c.), then filtered, and the solid [0·48 g.; m. p.

160° (decomp.)] recrystallised from aqueous ethanol (charcoal), giving semicarbazide hydrochloride, colourless plates, m. p. 169° (decomp.), further identified by conversion into benzaldehyde semicarbazone, m. p. and mixed m. p. 214°.

The solvent was evaporated from the chloroform-soluble fraction, and the remaining oil distilled (bath-temperature 230—240°) yielding methyl thiolbenzoate as a colourless liquid, identified by alkaline hydrolysis to methanethiol and benzoic acid, m. p. and mixed m. p. 122°.

1-(4-Ethanesulphonyl-α-methylthiobenzylidene)semicarbazide (6·0 g.) was hydrolysed by boiling it under reflux with concentrated hydrochloric acid (60 c.c.) and ethanol (180 c.c.) for 30 minutes, the solution evaporated to dryness at room temperature and the residue triturated with water (40 c.c.). The undissolved solid was filtered off, washed, and dried, yielding *methyl 4-ethanesulphonylthiolbenzoate* (4·6 g.; m. p. 66°) which formed colourless needles, m. p. 87—88°, from light petroleum (b. p. 80—100°) or from *iso*propyl alcohol (Found : C, 48·8; H, 4·9. $C_{10}H_{12}O_3S_2$ requires C, 49·2; H, 4·9%).

The aqueous filtrate, on evaporation to dryness at room temperature, yielded semicarbazide hydrochloride (2·2 g.), m. p. 161—164° (decomp.), raised by recrystallisation from aqueous ethanol to 168° (decomp.) undepressed by an authentic specimen.

Attempted Decomposition with Alkali.—1-α-Methylthiobenzylidenesemicarbazide (1·0 g.) after 12 hours' boiling under reflux with a solution of potassium hydroxide (1·0 g.) in ethanol (30 c.c.), followed by partial evaporation of the solvent and addition of water, yielded only the starting material (0·6 g.; m. p. 154°).

Effect of Heat.—1-α-Methylthiobenzylidenesemicarbazide (0·8 g.) was heated at 210—215° for 1·5 hours. Methanethiol was rapidly evolved and the melt resolidified. The solid (0·5 g.) dissolved almost entirely in 5N-sodium hydroxide. Precipitation by acid and recrystallisation from ethanol gave 3-hydroxy-5-phenyl-1 : 2 : 4-triazole, m. p. 316° (Found : C, 59·65; H, 4·0. Calc. for $C_8H_7ON_3$: C, 59·65; H, 4·35%). Young and Witham (*J.*, 1900, **77**, 228) give m. p. 321—322°.

Reactions of methiodides with ammonia and amines.

Reaction with Aqueous Ammonia.—4-α-Methylthiobenzylidenemorpholinium iodide (10 g.) was shaken at room temperature with ammonia solution (100 c.c.; *d* 0·935). The methiodide immediately dissolved and an oil separated which solidified in a few minutes. There was a strong smell of methanethiol. On mechanical shaking for 16 hours, most of the solid redissolved. The filtered solution gave with aqueous lithium picrate a copious precipitate of benzamidine picrate, m. p. and mixed m. p. 235° after crystallisation from water.

In a duplicate experiment, the reaction was stopped when the oil solidified, and the solid was immediately filtered off, washed with water, and dried in a vacuum-desiccator. It appeared to be decomposed by atmospheric moisture, producing a strong smell of methanethiol. A little was decomposed by boiling 50% aqueous ethanol (2 hours) with the liberation of much methanethiol. On cooling, yellow hair crystals separated. After recrystallisation from ethanol, these were identified as thiobenzomorpholide, m. p. 136°, undepressed by an authentic specimen. The aqueous-alcoholic mother-liquor was evaporated to dryness and the residual oil solidified on being rubbed. Recrystallisation from ethanol gave benzomorpholide, m. p. 72°, undepressed by a specimen m. p. 74°.

Another portion of the solid intermediate compound was shaken mechanically at room temperature for 21 hours with ammonia solution (*d* 0·935). A small insoluble residue was filtered off and, after recrystallisation from ethanol, yielded yellow needles of thiobenzomorpholide, m. p. 137°. The filtrate was evaporated to dryness *in vacuo* and the residue, when dissolved in water, gave with lithium picrate solution a precipitate of benzamidine picrate, m. p. and mixed m. p. 232° after recrystallisation from water.

Some of the solid intermediate product was dissolved in acetone, and a few drops of constant-boiling hydriodic acid were added, excess being avoided. The solution was poured into much ether, and the precipitated yellow oil slowly solidified on being rubbed. It was washed by decantation with ether and purified twice by precipitation from absolute ethanol with ether, giving 4-α-methylthiobenzylidenemorpholinium iodide, m. p. 158° (decomp.), undepressed by the original compound.

The solid intermediate product, when washed with water and re-dissolved in aqueous ethanol, gave a solution of pH 8—9.

Reaction with Aniline.—4-α-Methylthiobenzylidenemorpholinium iodide (24·5 g.) was shaken mechanically at room temperature with absolute ethanol (70 c.c.) and redistilled aniline (7 c.c.). The reaction mixture became warm and a solid soon began to crystallise. After 16 hours, the

product was filtered off, washed with small quantities of ethanol, and dried. The colourless material (24·1 g.) was purified by recrystallisation from ethanol and from water, giving needles or hair crystals of *N-phenylbenzimidoylmorpholide hydriodide*, m. p. 288—289° (decomp.) (Found : C, 51·9; H, 4·75; N, 7·35. $C_{17}H_{19}ON_2I$ requires C, 51·8; H, 4·8; N, 7·1%).

Reaction with Morpholine.—4-α-Methylthiobenzylidenemorpholinium iodide (22·0 g.) and morpholine (15 c.c.) were heated on the steam-bath, moisture being excluded. A vigorous reaction with evolution of methanethiol occurred almost at once and heating was continued for 2 hours. The mixture was cooled and the solid triturated with ether, filtered off, washed with ether, and dried. The product (23·5 g.) was purified by recrystallisation from ethanol, giving pale yellow needles of *4-α-morpholinobenzylidenemorpholinium iodide*, m. p. 291° (decomp.) (Found : C, 46·75; H, 5·3; N, 7·4. $C_{15}H_{21}O_2N_2I$ requires C, 46·4; H, 5·4%; N, 7·2%). It was soluble in water to the extent of about 1% at room temperature, giving an almost neutral solution.

The *picrate* formed deep yellow leaflets (from ethanol), m. p. 153—154° (Found : C, 51·0; H, 4·7. $C_{21}H_{23}O_9N_5$ requires C, 51·5; H, 4·7%).

The experiment of Rogers (*loc. cit.*), with 4-(1-methylthio-2-phenylethylidene)morpholinium iodide and morpholine, was repeated, and there was obtained ββ-dimorpholinostyrene, m. p. 134—135° (Found: C, 70·5; H, 8·2. Calc. for $C_{16}H_{22}O_2N_2$: C, 70·05; H, 8·0%) (Rogers, *loc. cit.*, gives m. p. 131—132°).

Hydrolysis of 4-α-Morpholinobenzylidenemorpholinium Iodide.—The iodide (3·0 g.) was shaken mechanically for 2 days with N-sodium hydroxide (7·7 c.c., 1 mol.), water (2·3 c.c.), and chloroform (20 c.c.). The chloroform layer was separated and dried (Na_2SO_4), and the solvent evaporated. The residual oil solidified yielding benzomorpholide (1·4 g., 95%), m. p. 72°.

Dithioesters.

Methyl Dithioacetate.—4-1-Methylthioethylidenemorpholinium iodide (47 g.) was added to dry methanol (300 c.c.) saturated at 0° with dry hydrogen sulphide. Crystals of morpholine hydriodide were deposited almost immediately. The cooling-bath was removed and passage of hydrogen sulphide continued for 3 hours, whereafter the mixture was set aside for 2 days. Distillation afforded a mixture of methyl dithioacetate and methanol, and a residue of large crystals of morpholine hydriodide which were collected, washed with ether, and dried (34·4 g., 98%; m. p. 206°). Recrystallisation from ethanol raised the m. p. to 209—210°, undepressed by an authentic sample prepared from morpholine and hydriodic acid.

The deep yellow methanolic distillate was added to benzylamine (27 c.c.) with shaking, and the solution, now colourless, was kept for 16 hours and the methanol evaporated. Trituration of the oily residue with cold 2N-hydrochloric acid (75 c.c.) afforded thioacetobenzylamide as colourless crystals (20·8 g., 77%; m. p. 63°). Worrall (*J. Amer. Chem. Soc.*, 1928, **50**, 1459) gives m. p. 62—63°.

Methyl Dithiobenzoate.—Thiobenzomorpholide (50 g.), dry, methanol-free acetone (250 c.c.), and methyl iodide (18 c.c.) were boiled together under reflux for 20 minutes, during which the methiodide separated. The mixture was cooled, diluted with dry pyridine (50 c.c.) saturated with dry hydrogen sulphide for 6 hours, and kept for 14 hours. Most of the acetone was then evaporated under reduced pressure and the residue poured on ice and dilute hydrochloric acid. The methyl dithiobenzoate was extracted with ether and obtained as a bright red oil (26·1 g., 64%), b. p. 118°/3 mm., 105°/1 mm.

The ester was also prepared from the methiodide in absolute ethanol saturated with hydrogen sulphide in 69% yield, b. p. 123°/4 mm.

Methyl Phenyldithioacetate.—Crude phenylthioacetomorpholide (50 g.) (from the Willgerodt reaction with acetophenone) was converted into the methiodide which was filtered off, washed with ether, and dissolved at once in dry pyridine (75 c.c.). The solution was saturated with hydrogen sulphide, kept for 24 hours, and worked up as previously, affording methyl phenyldithioacetate as an orange oil, b. p. 120°/1 mm. (18 g., 44%).

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778. *Dealkylation and Hydrolysis of Alkyl Phosphites, Phosphates, and Phosphonates.*

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The reaction of the butyl phosphates, tri-2-octyl phosphate, and di-2-octyl ethylphosphonate with hydrogen halides is comparable with that of the halides with *n*-butyl hydrogen phosphite, the much quicker rate of dealkylation (one group) of trialkyl phosphites (Gerrard and Whitbread, *J.*, 1952, 914) being brought into marked contrast. High predominance of inversion accompanied the formation of 2-halogeno-octane from the phosphate and phosphonate. From the degree of retention of configuration of the octan-2-ol formed, it appeared that acyl–oxygen fission occurred in alkaline and alkyl–oxygen fission in the acid hydrolysis of the phosphate and phosphonate, although under either condition the phosphite and hydrogen phosphite were hydrolysed to alcohol having a high degree of retention of configuration. In view of the slow hydrolysis of the phosphate and phosphonate, hydrogen bromide affords a ready means of removing alkyl groups, and especially is this of interest in the preparation of alkylphosphonic acids without incursion of water.

Blumenthal and Herbert (*Trans. Faraday Soc.*, 1945, **41**, 611) concluded that acyl–oxygen fission had occurred in the alkaline hydrolysis of trimethyl phosphate, because the methyl alcohol was not enriched in ^{18}O. Although it was realised that the results were not entirely unambiguous, it was believed that in acid hydrolysis alkyl–oxygen fission (70%) had occurred.

Experimental

Interaction of Hydrogen Halides and Tributyl Phosphates.—The esters were prepared in a pure condition by means of pyridine and phosphorus oxychloride (Gerrard, *J.*, 1940, 1464). Into the *n*-butyl ester (11·8 g.) dry hydrogen chloride was passed for 6 hours at 17°, the effluent gas being passed through a U-tube maintained at −80°, which was also employed to condense butyl chloride distilled from the final reaction mixture at 15°/1 mm. After the mixture had been at 17° for 12 hours, from it was obtained *n*-butyl chloride (0·43 mol.), b. p. 77° (Found: Cl, 38·1. Calc. for C_4H_9Cl: Cl, 38·3%). *n*-Butyl chloride (0·90 mol.), b. p. 77° (Found: Cl, 37·9%), was similarly obtained from the ester (4·2 g.) after the gas had been passed for 4·5 hours at 50—60° and the mixture kept at 16° for 12 hours. At evenly spaced intervals during 3 weeks the gas was passed into the ester (4·27 g.) for 10·6 hours at 50—60° and then for 34·5 hours at 90—100°, giving *n*-butyl chloride (2·75 mols.), b. p. 77° (Found: Cl, 38·0%). Tri-*iso*butyl phosphate (15·0 g.), after being saturated with the gas (8 hours) at 25° (1·71 mols. absorbed) and kept at 25° for 75 days, afforded the chloride (0·55 mol.), b. p. 68—69° (Found: Cl, 38·0%). Tri-*sec.*-butyl phosphate (12·60 g.) under the same conditions gave the chloride (0·87 mol.), b. p. 68° (Found: Cl., 37·9%). Similarly the *iso*butyl ester (14·0 g.) and hydrogen bromide (2·07 mols. absorbed) afforded *iso*butyl bromide (1·27 mols.) b. p. 90—91° (Found: Br, 58·1. Calc. for C_4H_9Br: Br, 58·4%). The *sec.*-butyl ester (17·6 g.) gave *sec.*-butyl bromide (2·05 mols.), b. p. 91—92° (Found: Br, 57·6%), hydrogen bromide (2·21 mols.) being absorbed during the passage of the gas. Into the *n*-butyl ester (4·3 g.) at 20° hydrogen bromide was passed for 3 hours (2·02 mols. being absorbed) and *n*-butyl bromide (1·23 mols.), b. p. 100° (Found: Br, 58·2%), was obtained.

Hydrogen Bromide and (+)-Tri-2-octyl Phosphate.—Into the ester (2·0 g.) (from ROH, α_D^{20} +7·64°, l = 1 dm.) the gas was passed for 48 hours at 20°, and (−)-2-bromo-octane (2·48 g., 2·5 mols.), b. p. 61°/7 mm., α_D^{14} −27·8° (Found: Br, 41·4. Calc. for $C_8H_{17}Br$: Br, 41·4%), and a residue of phosphoric acid (0·46 g.) (Found: P, 30·2. Calc.: P, 31·6%) were obtained. The bromide (2·33 g., 2·4 mols.), b. p. 76°/15 mm., α_D^{14} −26·80° (Found: Br, 41·3%), and phosphoric acid (0·46 g.) were obtained after 9 hours at 45—50°; and after 6 hours at 95—100°, the bromide (2·48 g., 2·5 mols.), b. p. 63°/8 mm., α_D^{14} −24·3° (Found: Br, 41·4%), and phosphoric acid (0·46 g.) were obtained.

Hydrogen Halides and Di-2-octyl Ethylphosphonate.—Into the phosphonate (Gerrard and Green, *J.*, 1951, 2550) the gas was passed continuously for the time and at the temperature stated in Table 1. The calculated weights for $C_8H_{17}X$ are Cl 3·56 g. (Cl, 23·9%), Br 4·62 g. (Br, 41·4%), I 5·75 g. (I, 52·9%). In the chloride and bromide experiments, gas was removed from the mixture at 1 mm. before distillation; in the iodide experiments treatment with water was given.

TABLE 1. *Dealkylation of di-2-octyl ethylphosphonate* (4·0 g.) (*from* ROH, α_D^{18} −8·00°).

Time (hours)	Temp.	C_8H_{17}·Hal: Yield (g.)	B. p./mm.	α_D (temp.)	Found : Hal, %
Hydrogen chloride.					
336	20—25°	0·62	59·5°/13	+27·6° (21°)	23·5
106	50—55	2·17	59°/12	+24·28 (16)	23·7
21·5	95—100	2·67	60°/14	+25·20 (24)	23·6
Hydrogen bromide.					
48	20—25	4·56	73°/14	+30·70 (20)	41·2
8	45—50	3·96	,,	+31·72 (20)	41·4
11	70—75	4·38	72·5°/13	+30·6 (23)	41·4
Hydrogen iodide.					
7·5	20—25	4·65	84·5°/11	+39·44 (20)	52·3
7	−15	2·18	87·5°/13	+47·72 (20)	52·7
14·5	50—55	4·54	90·5°/15	+23·70 (23)	52·0

TABLE 2. *Hydrolysis of 2-octyl esters containing phosphorus.*

No.	Ester (g.)		Medium	Time of reflux (hours)	Alcohol: Weight (g.)	B. p./mm.	α_D (Found)	α_D (original)	n_D
1	$(RO)_3P$	(4·0)	N-HCl (aq.)	24	1·47	81·5°/17	−8·12° (16·5°)	−8·10° (24°)	1·4272 (16·5°)
2	,,		N-KOH (aq.)	,,	2·26	81°/16	−8·08 (16·5)	,,	1·4272 (16·5)
3	$(RO)_2P$·OH	(4·0)	N-HCl (aq.)	28	1·56	75°/13	+6·92 (21)	+7·4 (23)	1·4268 (20)
4	,,		N-KOH (aq.)	28	1·37	74°/13	+7·24 (19)	,,	1·4265 (20)
5	$(RO)_3PO$	(2·0)	N-KOH (aq.)	24	0·26	81°/18	+6·12 (11)	+7·67 (19)	1·4299 (12)
6	,,		2N-KOH (EtOH)	37	0·32	68°/7	+6·56 (15)	,,	1·4275 (16)
7	,,		N-HCl (aq.)	24	0·28	75°/13	+4·48 (11)	,,	1·4299 (10)
8	$Et·PO(OR)_2$	(3·0)	N-KOH (aq.)	25	0·28	77°/15	−7·32 (15)	−8·0 (20)	1·4292 (15)
9	,,		N-HCl (aq.)	25	0·31	74°/13	−1·06 (15)	,,	1·4295 (15)
10	,,		N-KOH (aq. EtOH)	24	0·35	74°/12	−7·92 (15)	,,	1·4282 (15)
11	,,		2N-KOH (EtOH)	38	0·44	82°/18	−7·08 (15)	,,	1·4268 (17)
12	,,		N-HCl (aq. EtOH)	24	0·41	73°/11	−0·92 (15)	,,	1·4272 (15)

Weights of recovered esters were : (5) 0·7, (6) 0·5, (7) 0·64, (8) 1·21, (9) 1·69, (10) 1·77, (11) 1·1, and (12) 1·48 g.

Hydrolysis of 2-Octyl Esters.—The ester was heated under reflux with the medium (50 c.c.) for the time stated, the alcohol then being isolated from the dried ethereal extract of the steam-distillate. Data are recorded in Table 2 and in the following notes. (1—4) The esters were prepared as described by Gerrard (*J.*, 1944, 85). (5) The phosphate had b. p. 145°/0·05 mm., n_D^{15} 1·4412, α_D^{22} +20·68° (all rotatory powers are for $l = 1$ dm.) (from ROH, α_D^{19} +7·67°) (Found: C, 66·5; H, 11·6. Calc. for $C_{24}H_{51}O_4P$: C, 66·4: H, 11·7%). Solvent termed aq. EtOH contained 25 c.c. of each liquid. When 2N-ethanolic hydrochloric acid was used the phosphate [see (5)] after 37 hours afforded 2-chloro-octane (0·66 g.), b. p. 50°/9 mm., α_D^{15} −14·65°, and the alcohol (0·2 g.), b. p. 68—69°/9 mm., α_D^{15} +1·60°, n_D^{16} 1·4265; and the phosphonate [see (8)] after 38 hours afforded 2-chloro-octane (1·12 g., b. p. 49°/8 mm., α_D^{10} +15·24°).

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779. *Trifluoromethylbenziminazoles.*

By A. SYKES and J. C. TATLOW.

FOR other studies, benziminazoles with trifluoromethyl substituents were required, and, since derivatives of this type have not yet been reported, the synthesis of two such compounds is herein described. 3-Amino-2- and -4-nitrobenzotrifluoride were prepared as described by Rouche (*Bull. Acad. roy. Belg., Classe Sci.*, 1927, **13**, 346) and Pouterman and Girardet (*Helv. Chim. Acta*, 1947, **30**, 107) by nitration of *m*-acetamidobenzotrifluoride with nitric acid–acetic anhydride, deacetylation of the product, and separation of the mixture. These nitro-amines, when reduced with stannous chloride in hydrochloric acid, yielded the corresponding phenylenediamines, 2 : 3- and 3 : 4-diaminobenzotrifluoride, respectively. The latter has been made by Whalley (*J.*, 1950, 2792), using hydrogen and palladium–charcoal. 2 : 3-Diaminobenzotrifluoride, when treated with formic acid according to Phillips (*J.*, 1928, 2393), gave 4-trifluoromethylbenziminazole; with benzil in methyl alcohol, 2 : 3-diphenyl-5-trifluoromethylquinoxaline was formed. These reactions confirm the structure assigned by the original authors to the parent nitro-amine. From the 3 : 4-diamine, 5-trifluoromethylbenziminazole was prepared in a similar manner.

EXPERIMENTAL

2 : 3-*Diaminobenzotrifluoride.*—Stannous chloride dihydrate (30 g.) in concentrated hydrochloric acid (60 c.c.) was added slowly to a warm solution of 3-amino-2-nitrobenzotrifluoride (5·0 g.) in ethyl alcohol (40 c.c.), and the mixture was refluxed for 30 minutes, before being poured into water. The solution was made strongly alkaline with aqueous sodium hydroxide and extracted with ether, and the extracts were washed with water, separated, dried ($MgSO_4$), filtered, and concentrated to leave a residue, which, on distillation under diminished pressure, gave 2 : 3-*diaminobenzotrifluoride* (2·8 g., 66%), b. p. 125°/14 mm., m. p. 41° (Found: C, 47·5; H, 3·8; F, 32·0. $C_7H_7N_2F_3$ requires C, 47·7; H, 4·0; F, 32·4%).

The diamine, with acetic anhydride and glacial acetic acid (30 minutes' refluxing), gave the *diacetyl* derivative, m. p. 228—229° (from ethyl alcohol) (Found: C, 50·9; H, 4·2. $C_{11}H_{11}O_2N_2F_3$ requires C, 50·8; H, 4·3%).

2 : 3-*Diphenyl-5-trifluoromethylquinoxaline.*—The 2 : 3-diamine (0·35 g.) and benzil (0·40 g.) were refluxed in methyl alcohol (10 c.c.) for 30 minutes, the solution was cooled, and the precipitate recrystallised from methyl alcohol to give the *quinoxaline* (0·38 g., 57%), m. p. 139° (Found: C, 72·1; H, 3·9. $C_{21}H_{13}N_2F_3$ requires C, 72·0; H, 3·7%).

4-*Trifluoromethylbenziminazole.*—2 : 3-Diaminobenzotrifluoride (4·40 g.), 90% formic acid (1·85 c.c.), and 4N-hydrochloric acid (25 c.c.) were refluxed together for 45 minutes, and the solution was then cooled and neutralised with ammonia solution, the resulting precipitate being recrystallised from water (charcoal), to give 4-*trifluoromethylbenziminazole* (2·06 g., 44%), m. p. 192·5° (Found: C, 51·6; H, 2·6; F, 31·0. $C_8H_5N_2F_3$ requires C, 51·6; H, 2·7; F, 30·6%).

3 : 4-*Diaminobenzotrifluoride.*—3-Amino-4-nitrobenzotrifluoride, reduced by the method described above, gave 3 : 4-diaminobenzotrifluoride (86%), m. p. 58°. Whalley (*loc. cit.*) recorded m. p. 58°.

5-*Trifluoromethylbenziminazole.*—The 3 : 4-diamine (5·20 g.), 90% formic acid (2·2 c.c.), and 4N-hydrochloric acid (30 c.c.), treated as before, afforded 5-*trifluoromethylbenziminazole* (1·90 g., 35%), m. p. 119° (Found: C, 51·3; H, 2·8; F, 30·8%).

The authors are indebted to the Imperial Smelting Corporation Ltd. for a gift of benzotrifluoride. One of them (A. S.) thanks the Department of Scientific and Industrial Research for the award of a maintenance grant.

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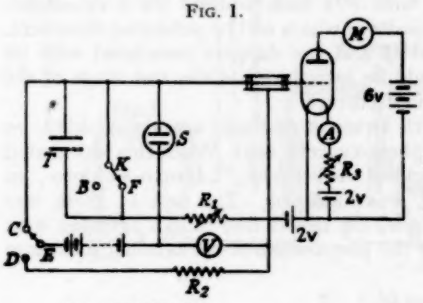
EDGBASTON, BIRMINGHAM, 15. [*Received, April 24th*, 1952.]

780. *The Electrical Conductivity of Liquid Dinitrogen Tetroxide.*

By C. C. ADDISON and J. LEWIS.

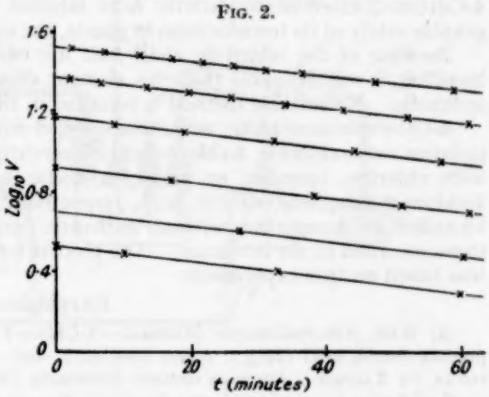
IN measurements of the electrical conductivity of liquid dinitrogen tetroxide, described by Addison, Allen, Bolton, and Lewis (*J.*, 1951, 1289), the potential difference between the electrodes did not exceed 2 v. No evidence of a decomposition potential was obtained and no variation in the electrical resistance was observed, when this potential difference was varied within the 0—2 v range. Various mechanisms of electrical conduction were considered; one attractive possibility involved the passage of electric current through the liquid by the ionisation of the NO_2 molecule to the NO_2^+ ion, and the subsequent transfer of electrons along a chain of NO_2 groups. Since the ionisation potential for the NO_2

FIG. 1.



R_1 = 50,000 *Ohms.*
R_2 = 50,000 *Ohms.*
R_3 = 20 *Ohms.*
S = *Conductivity cell.*
T = *Condenser, capacity* 0·01 μF.

FIG. 2.



molecule in the gaseous phase is 12·3 v (Price and Simpson, *Trans. Faraday Soc.*, 1941, **37**, 106), it appeared possible that a different value for the conductivity might be obtained if a higher potential difference was applied across the electrodes. The conductivity has therefore been determined over the range 2—32 v. The results given below show that the conductivity has a constant value throughout the whole of this range. The values are of the same order as those obtained in the 0—2 v range and hence the mechanism referred to above is now considered to be unlikely.

The conductivity cell, the handling techniques, the precautions against surface conduction, the electrometer valve characteristics, and the method of preparation of pure liquid tetroxide were those already described by Addison *et al.* (*loc. cit.*). The electrical circuit employed is shown in Fig. 1. A potential of −2 v was applied to the valve grid by placing key K at F. The anode current (the " zero " reading) registered on the microammeter M was noted, and K was transferred to position B. A potential of −32 v was applied to the grid by switching the key E to position C; E was then moved to point D, and the resistance R_1 varied to restore the zero reading on M. Under these conditions, the extra negative potential applied was counterbalanced by the potential introduced by the potentiometer circuit. The voltage across R_1 required to do this was measured by a high-resistance voltmeter V. By varying R_1, the voltmeter reading was then decreased in steps of 1 v, and at each stage the time taken for the grid potential to decay to this voltage was noted.

If the resistance of the liquid remains constant over the voltage range employed, then a graph of log V against time t will be a straight line, since $V_t = V_0 e^{-t/CR}$. The experimental

results in Fig. 2 show that this is the case. The lines in Fig. 2 represent sections of one continuous straight line extending over the range 2—32 v.

The table gives the electrical specific conductivities (κ in ohm.$^{-1}$ cm.$^{-1}$ $\times$ 10^{12}) of three separate preparations of liquid dinitrogen tetroxide, determined from the slope of the appropriate (log V) $-$ t line. The second value in each case is a duplicate measurement taken several hours after the first.

Prep. no.	Temp.	κ	Prep. no.	Temp.	κ	Prep. no.	Temp.	κ
1	21°	5·20, 5·24	2	21°	4·31, 4·31	3	20°	1·14, 1·19

These conductivity values lie within the range (1·24—8·08 $\times$ 10^{-12}) of values obtained in measurements carried out between 0 and 2 v.

The authors are indebted to Dr. H. C. Bolton for valuable advice and discussion.

THE UNIVERSITY, NOTTINGHAM. [*Received, May 15th*, 1952.]

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781. 4-*Chloro-2-iodophenoxyacetic Acid labelled with* ^{131}I.

By R. L. JONES.

4-CHLORO-2-IODOPHENOXYACETIC ACID labelled with ^{131}I was required for a radioautographic study of its translocation in plants, the results of which will be published elsewhere.

Because of the relatively short half life of ^{131}I and the dangers associated with its handling, it was desirable that this element should be introduced at the last stage of the synthesis. No suitable method is recorded in the literature.

4-Chlorophenoxyacetic acid, when boiled with aqueous mercuric acetate, yielded, on isolation as the chloride, 4-chloro-2-chloromercuriphenoxyacetic acid. When this was heated with chlorine, bromine, or iodine in acetic acid 2 : 4-dichloro-, 2-bromo-4-chloro-, or 4-chloro-2-iodophenoxyacetic acid, respectively, was obtained. The first of these was identified by comparison with an authentic sample, the others had m. p.s agreeing with those recorded in the literature. The process for the preparation of the labelled substance was based on this experiment.

EXPERIMENTAL

(a) *With Non-radioactive Material.*—*4-Chloro-2-chloromercuriphenoxyacetic acid.* 4-Chlorophenoxyacetic acid (20 g.), water (500 c.c.), and mercuric acetate (32 g.) were boiled under reflux for 2 hours. Aqueous sodium hydroxide (30%) was then added to the cooled mixture until all but a trace of solid was dissolved, the solution was treated with charcoal and filtered, and the filtrate acidified with hydrochloric acid. The flocculent precipitate was washed, dried at 80° (37 g.), and crystallised first from acetic acid (30 c.c.) and then from 35% aqueous ethanol. The *acid* had m. p. 189—190°, unchanged by further crystallisation (21·4 g.) (Found : Hg, 46·3; Cl, 15·0%. $C_8H_6O_3Cl_2Hg$ requires Hg, 47·5; Cl, 17·2%). This substance decomposes slowly on storage; material stored for 4 weeks was, however, satisfactory for the preparation of 4-chloro-2-iodophenoxyacetic acid.

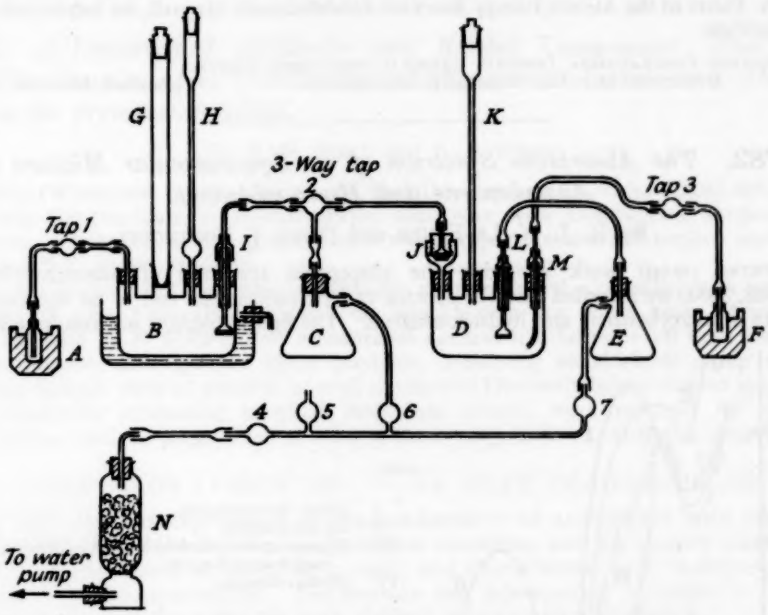
2 : 4-*Dichlorophenoxyacetic acid.* 4-Chloro-2-chloromercuriphenoxyacetic acid (4·2 g.), m. p. 185—186°, was added to acetic acid (30 c.c.) containing chlorine (0·71 g.). After 1 hour the mixture was heated slowly to 90° (2 hours), then poured into water and filtered, the insoluble material was extracted with warm dilute sodium hydroxide and filtered, and the filtrates were acidified with hydrochloric acid. The precipitate was crystallised from water and then had m. p. 137—138°, undepressed on admixture with an authentic sample of 2 : 4-dichlorophenoxyacetic acid.

2-Bromo-4-chlorophenoxyacetic acid, m. p. 138–139°, was similarly obtained from bromine (1·6 g.) and the mercurial (4·2 g.) in glacial acetic acid (37 c.c.). 4-Chloro-2-iodophenoxyacetic acid, m. p. 140° (Newman, Fones, and Renoll, *J. Amer. Chem. Soc.*, 1947, **69**, 718, give m. p. 136—140°) (Found : C, 30·4; H, 2·1; Cl, 11·3; I, 40·2. Calc. for $C_8H_6O_3ClI$: C, 30·7; H, 1·9; Cl, 11·4; I, 40·6%), was obtained similarly.

(b) *With Radioactive Material.*—The apparatus, shown in the diagram, was mounted on a sheet of lead $\frac{1}{2}''$ $\times$ 8″ $\times$ 36″, behind a permanent lead screen, $\frac{1}{2}''$ $\times$ 20″ $\times$ 36″, in a fume cupboard fitted with $\frac{1}{4}''$ thick sliding lead doors. *G*, *H*, and *K* (see below) extended above the screen.

I and *L* were 9-mm. diameter sintered-glass disc filters of grade 3 porosity, which could be raised and lowered, vacuum being maintained by rubber sleeves. The tube *M* could be similarly handled. *J* was an auxilliary filter made of Perspex, taking four 1-cm. filter circles of Whatmans No. 42 grade filter paper. The scrubbing tower *N* was packed with pumice stone soaked in a solution of glycerine, water, and potassium iodide.

The sample, from the Atomic Energy Research Establishment, Harwell, contained 500 millicuries of ^{131}I and consisted of a trace of sodium iodide in 20 c.c. of water together with 10—20 mg. of sodium sulphite and small amounts of sulphate. It was sucked from its container in the lead safe *A* into the 100-c.c. four-necked round-bottomed flask *B*, by applying suction *via I* (in the raised position) and the 100-c.c. Buchner flask *C*. The sample was washed in with water (5 c.c.). The vacuum was released and an aqueous solution (5 c.c.) of potassium iodide (10·2 g. made up to 250 c.c.) and sulphuric acid (5 c.c.; 150 c.c. of 98% sulphuric acid diluted with 100 c.c. water) added *via H* which was jointed to *B* with a rubber bung and had a bubble blown in it about 1″ above *B* to avoid the rise, by capillarity, of bubbles containing



radioactive material. The mixture was shaken and aqueous potassium dichromate (8 c.c.; 3·02 g. in 250 c.c.) added *via H*. The mixture was again shaken and set aside overnight at room temperature. The liquors were then sucked through *I* (lowered) into *C* and the residual iodine was washed with water (2 × 5 c.c.) (collected in *C*). Meanwhile, 4-chloro-2-chloromercuriphenoxyacetic acid (0·20 g.), m. p. 189—190°, was ground to a coarse powder, wetted with glacial acetic acid (0·5 c.c.), and moulded by being frozen (ethanol–solid carbon dioxide) in a glass tube. The frozen pellet was transferred to *G* (a ½″ diameter glass tube, jointed to *B* with a B.14 ground-glass joint) and thence by gravity into *B*. Acetic acid (2·5 c.c.) was added *via H*, and the contents of *B* heated (bath-temp. 90°) for 1 hour and then cooled. After 20 minutes, water (20 c.c.) was added, the mixture well shaken, and set aside for 15 minutes. Tube *I* was then lowered and the liquors were filtered into *C*. The residue of mercuric iodide and 4-chloro-2-iodophenoxyacetic acid was washed with water (2 × 5 c.c.) (collected in *C*), and then extracted with a solution of (5 c.c.) of triethanolamine (20 g. made up to 250 c.c. with water) with intermittently shaking for 5 minutes; the liquors were sucked into the second 100 c.c. four-neck flask *D via I* (lowered) and *J*. The residue in *B* was washed with water (2 × 5 c.c.), which was added to the solution already in *D*. Hydrochloric acid (5 c.c.) (30 c.c. of acid, *d* 1·16, made up to 250 c.c. with water) was added *via K*; the mixture was shaken, and, after 10 minutes, the liquors were filtered into the 100-c.c. Buchner flask *E via L* (lowered). The

white solid remaining was washed with water (2 × 5 c.c.), and ethanol (3 c.c.; 98%) was added. *D* was shaken until dissolution was complete; any solid sticking to *L* was washed off by gently blowing air through it in the lowered position. The solvents were then removed by drawing a stream of dry air ($CaCl_2$), through *K* and *L* (raised), over the ethanolic solution for 16 hours. Ethanol (1 c.c.; 98%) was added, and *D* was shaken until dissolution of the contents was complete. Olive oil (40 c.c.) was then added and shaking continued until a homogeneous solution was obtained; this was blown into the container in the lead safe *F*.

Yield and Quality of Product.—It was not possible to estimate the purity of the radioactive product because of the hazard involved in the isolation of the undiluted solid material; monitoring indicated 150 millicuries. In the many practice runs carried out with non-radioactive material, however, the yield was 0·1 ± 0·01 g. (from 4-chloro-2-chloromercuriphenoxyacetic acid, 0·20 g.), melting sharply at 139—140°: and the radio-active solution produced the expected biological response when applied to plants.

The author thanks Drs. W. A. Cowdrey, W. R. Boon, and Mr. D. Doxey of this Company and Dr. Faires of the Atomic Energy Research Establishment, Harwell, for helpful advice and collaboration.

RESEARCH LABORATORIES, IMPERIAL CHEMICAL INDUSTRIES LIMITED,
DYESTUFFS DIVISION, BLACKLEY, MANCHESTER. [*Received, May 21st,* 1952.]

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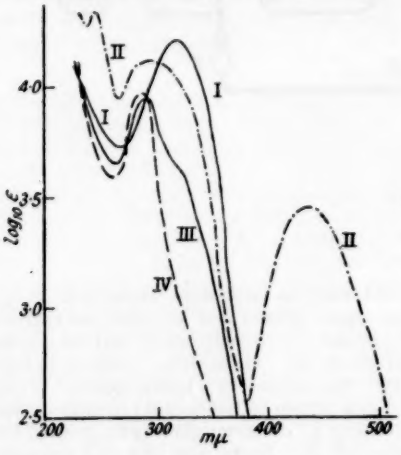
782. *The Absorption Spectrum of an Equimolecular Mixture of Azoxybenzene and Hydrazobenzene.*

By R. J. W. LE FÈVRE and (MISS) J. NORTHCOTT.

FOLLOWING recent work involving the absorption spectrum of *trans*-azoxybenzene (*J.*, 1952, 3384) we recorded also the spectra of hydrazobenzene and of an equimolecular mixture of azoxybenzene and hydrazobenzene. The figure displays our results (obtained



I. trans-*Azoxybenzene.*
II. cis-*Azobenzene.*
III. *Equimolecular mixture of* trans-*azoxybenzene and hydrazobenzene.*
IV. *Hydrazobenzene.*

with a Beckman Photoelectric Spectrophotometer, model D.U. on M/1000-solutions in alcohol); for hydrazobenzene they are reconcilable with the earlier, cruder graphs published by Purvis and McCleland (*J.*, 1912, **101**, 1519) and Kato and Someno (*Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1937, **33**, 209).

The improbability that the equimolecular mixture just mentioned has been previously wrongly identified as *cis*-azobenzene (cf. Hodgson's suggestion to this effect, *J.*, 1948, 1097, and subsequent comment on it by Le Fèvre and Souter, *J.*, 1949, 1595) is further strengthened by the present spectral evidence. If the extinction coefficients for the mixture are calculated on the molecular weight basis of (Ph·N_2O·Ph + PhNH·NHPh)/2,

its absorption curve is seen to be nearly the mean of those of its constituents. Most pertinent, however, is the fact that the mixture, when fresh, lacks the visible colour characteristic of *cis*-azobenzene:

Substance	$\lambda_{max.}$	$\log_{10} \varepsilon_{max.}$	$\lambda_{max.}$	$\log_{10} \varepsilon_{max.}$
cis-Azobenzene *	280—315	4·1	440	3·45
trans-Azobenzene *	315	4·7	440—450	2·9
trans-Azoxybenzene	320	4·2	—	—
Hydrazobenzene	285	4·0	—	—

* Data relating to absorption in ethanol from Hausser (*Z. Naturforsch.*, 1950, **5***a*, 56).

Of course, on storage a yellow-orange tint develops in both the mixture and the hydrazobenzene; this is irreversible and is presumably due to oxidation by air.

UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, June 9th*, 1952.]

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783. αβ-*Unsaturated Aldehydes and Related Compounds. Part II.** *The Reaction of αβ-Unsaturated Aldehydes with Unsaturated Alcohols in the presence of Alkali.*

By R. H. HALL and E. S. STERN.

A PATENT (Whetstone, Smith, Norton, and Shell Development Co., U.S.P. 2,561,254/1951), describing the reactions of αβ-unsaturated aldehydes with unsaturated alcohols, has prompted publication of the present note which reports somewhat similar work (the subject of B.P. Appln. 6681/50).

The alkali-catalysed reaction of aliphatic αβ-unsaturated aldehydes with aliphatic alcohols to give β-alkoxy-aldehydes has been known for some time (Heyse and I.G. Farbenind., G.P. 554,949) but unsaturated alcohols had hitherto not been employed in this reaction, although the likely products, containing an aldehyde group and an ethylenic linkage, seem of possible interest as reactive intermediates for further syntheses. Such aldehydes, containing terminal methylene groups, were required for another investigation, and the preparation of a few of these compounds was therefore undertaken.

$$CH_2{:}CR''{\cdot}CH_2{\cdot}OH + CHR{:}CR'{\cdot}CHO \xrightarrow{\text{Alkali}} CH_2{:}CR''{\cdot}CH_2{\cdot}O{\cdot}CHR{\cdot}CHR''{\cdot}CHO$$

No difficulty was experienced in the condensation of acraldehyde with allyl and 2-methylallyl alcohols under the usual alkaline conditions and the desired alkenyloxy-aldehydes were isolated in about 50% yields and characterised as 2 : 4-dinitrophenylhydrazones and semicarbazones. The reaction was subsequently extended to crotonaldehyde and α-methylacraldehyde, each of which reacted with allyl alcohol.

Hydrogenation of the alkenyloxy-aldehydes over Adams's catalyst or over palladium–charcoal readily saturated the ethylenic linkage without affecting the aldehyde grouping and gave the corresponding saturated aldehydes, two of which were also prepared by condensing *n*-propanol with acraldehyde and crotonaldehyde, respectively. The two specimens of β-propoxypropaldehyde gave the same 2 : 4-dinitrophenylhydrazone and semicarbazone (mixed melting points); similar results were also obtained in the case of the two specimens of β-propoxybutaldehyde.

Experimental.—M. p.s and b. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss of Oxford.

β-*Allyloxypropaldehyde*. In a typical experiment, acraldehyde (170 ml.; equivalent to 126 g. of pure aldehyde) was added dropwise during about 2 hours to stirred allyl alcohol (500 ml.) containing 50% wt./vol. aqueous sodium hydroxide (3 g.) at −10° to −5°, the cold mixture was acidified with acetic acid (5 ml.) and phosphoric acid (1·5 g.), and then rapidly distilled under reduced pressure. The distillate, on careful fractionation, gave first allyl alcohol and then β-allyloxypropaldehyde (140 g., 55%), b. p. 55°/14 mm., n_D^{20} 1·4291 (Found: C, 62·85;

* *J.*, 1950, 490, is regarded as Part I.

H, 9·0. Calc. for $C_6H_{10}O_2$: C, 63·15; H, 8·85%). The *semicarbazone* crystallised from ethyl acetate–light petroleum (b. p. 40—60°) in fine needles, m. p. 109° (Found: C, 49·5; H, 7·8; N, 24·4. $C_7H_{13}O_2N_3$ requires C, 49·1; H, 7·65; N, 24·55%); the 2 : 4-dinitrophenylhydrazone crystallised from 95% ethanol in long, matted needles, m. p. 78·5° (Found: C, 49·5; H, 4·95; N, 18·9. Calc. for $C_{12}H_{14}O_5N_4$: C, 49·0; H, 4·8; N, 19·05%). Whetstone *et al.* (*loc. cit.*) record b. p. 71—73°/30 mm., n_D^{20} 1·4362, for the aldehyde and m. p. 73—73·5° for its 2 : 4-dinitrophenylhydrazone.

The aldehyde (57 g.) dissolved in ethanol (250 ml.) containing concentrated sulphuric acid (1 ml.) with spontaneous warming. The mixture was kept for 24 hours, then neutralised with sodium ethoxide in ethanol, and rapidly distilled under reduced pressure. The distillate on fractional distillation gave the *diethyl acetal* (73·5 g., 78%), b. p. 86°/13 mm., n_D^{20} 1·4219 (Found: C, 68·85; H, 10·5. $C_{10}H_{20}O_3$ requires C, 63·8; H, 10·7%).

On hydrogenation over Adams's catalyst (0·1 g.) in ethanol (50 ml.) at 16° and 740 mm., β-allyloxypropaldehyde (5 g.) rapidly absorbed hydrogen (1093 ml., *i.e.*, 1·01 mol.); absorption then slowed down considerably. Interruption of the reaction, filtration of the mixture, and fractional distillation of the filtrate gave β-*propoxypropaldehyde* (4·1 g.), b. p. 88°/90 mm., n_D^{20} 1·4100 (Found: C, 62·15; H, 10·4. $C_6H_{12}O_2$ requires C, 62·05; H, 10·4%), which was also obtained, in 23% yield, by the alkali-catalysed condensation of acraldehyde and propanol under the usual conditions. The aldehyde (prepared by either route) gave a 2 : 4-*dinitrophenylhydrazone*, which separated from ethanol in a felted mass of needles, m. p. 100·5° (Found: C, 49·05; H, 5·25; N, 19·1. $C_{12}H_{16}O_5N_4$ requires C, 48·65; H, 5·45; N, 18·9%), and a *semicarbazone*, which crystallised from ethyl acetate in fine needles, m. p. 130° (Found: C, 48·85; H, 8·8; N, 24·1. $C_7H_{15}O_2N_3$ requires C, 48·55; H, 8·75; N, 24·25%).

β-*Allyloxyisobutaldehyde*. Freshly distilled α-methylacraldehyde (70 g.) was added slowly at −5° to stirred allyl alcohol (230 g.) containing 40% aqueous sodium hydroxide solution (2·5 g.), the mixture was acidified with acetic acid and phosphoric acid, and rapidly distilled at about 120 mm. Fractionation of the distillate separated methylacraldehyde (28 g.), b. p. 31°/110 mm., n_D^{20} 1·4150, and allyl alcohol (202 g.), b. p. 51°/110 mm., n_D^{20} 1·4130, from the product, β-allyloxy*iso*butaldehyde (34 g., 50%), b. p. 63°/16 mm., n_D^{20} 1·4288 (Found: C, 65·7; H, 9·5. Calc. for $C_7H_{12}O_2$: C, 65·6; H, 9·45%). The *semicarbazone*, which crystallised from ethyl acetate–light petroleum in needles, had m. p. 88° (Found: N, 22·6. $C_8H_{15}O_2N_3$ requires N, 22·7%), and the 2 : 4-dinitrophenylhydrazone, which crystallised from 95% ethanol in flat needles, m. p. 72° (Found: C, 50·5; H, 5·3; N, 18·0. Calc. for $C_{13}H_{16}O_5N_4$: C, 50·65; H, 5·25; N, 18·2%). Whetstone *et al.* (*loc. cit.*) record b. p. 52—53°/10 mm., n_D^{20} 1·4320, for the aldehyde and m. p. 71·8—72·3° for its 2 : 4-dinitrophenylhydrazone.

Hydrogenation of the aldehyde (10 g.) in ethanol (100 ml.) over 5% palladium–charcoal catalyst (0·8 g.) resulted in the absorption of 1·00 mol. of hydrogen; gas absorption then ceased, and distillation of the filtered mixture gave β-*propoxyisobutaldehyde* (6·5 g.), b. p. 65°/28 mm., n_D^{20} 1·4100 (Found: C, 64·35; H, 10·9. $C_7H_{14}O_2$ requires C, 64·6; H, 10·9%). The aldehyde readily gave a 2 : 4-*dinitrophenylhydrazone*, which crystallised from methanol in flat needles, m. p. 71° (Found: C, 50·6; H, 6·0; N, 17·9. $C_{13}H_{18}O_5N_4$ requires C, 50·3; H, 5·85; N, 18·05%), and a *semicarbazone*, crystallising from ethyl acetate–light petroleum (1 : 3) in fine needles, m. p. 108—108·5° (Found: C, 51·45; H, 9·0; N, 22·2. $C_8H_{17}O_2N_3$ requires C, 51·35; H, 9·15; N, 22·45%).

β-*Allyloxybutaldehyde*. Slow addition, as above, of crotonaldehyde (105 g., 1·5 moles) to allyl alcohol (540 ml., 8 moles) containing 40% aqueous sodium hydroxide (5·8 g.), acidification of the solution with acetic acid and phosphoric acid, and fractional distillation of the product gave β-*allyloxybutaldehyde* (115·6 g., 60%), b. p. 77°/30 mm., n_D^{20} 1·4279 (Found: C, 65·9; H, 9·7. $C_7H_{12}O_2$ requires C, 65·6; H, 9·45%), the *semicarbazone* of which crystallised from ethyl acetate as fine clusters of needles, m. p. 109—109·5° (Found: C, 52·05; H, 8·25; N, 22·7. $C_8H_{15}O_2N_3$ requires C, 51·85; H, 8·15; N, 22·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from 95% ethanol in plates, m. p. 70—71° (Found: C, 50·9; H, 5·5; N, 18·0. $C_{13}H_{16}O_5N_4$ requires C, 50·65; H, 5·25; N, 18·2%).

On hydrogenation in ethanol over 5%-palladium–charcoal (1·0 g.) at 25° and 750 mm. the aldehyde (15·8 g.) rapidly absorbed hydrogen (3210 ml., 1·01 mol.); absorption then slowed down. Interruption of the reaction, filtration of the mixture, and fractional distillation of the filtrate gave β-*propoxybutaldehyde* (10·6 g.), b. p. 54°/16 mm., n_D^{20} 1·4110 (Found: C, 64·1; H, 11·15. $C_7H_{14}O_2$ requires C, 64·6; H, 10·85%), which was also obtained in 45% yield by the alkali-catalysed reaction, in the usual manner, of crotonaldehyde with propanol. The aldehyde (prepared by either route) gave a 2 : 4-*dinitrophenylhydrazone*, crystallising from methanol at

−15° in rosettes of needles, m. p. 54—55° (Found: C, 49·95; H, 5·5; N, 18·1. $C_{13}H_{18}O_8N_4$ requires C, 50·3; H, 5·85; N, 18·05%), and a *semicarbazone*, which crystallised from ethyl acetate–light petroleum (b. p. 40—60°) (1 : 6, by vol.) in needles, m. p. 88° (Found: C, 51·3; H, 8·95; N, 22·5. $C_9H_{17}O_3N_3$ requires C, 51·35; H, 9·15; N, 22·45%).

β-2-*Methylallyloxypropaldehyde.* Reaction, in the usual manner, of acraldehyde (75 ml.) and 2-methylallyl alcohol (256 g.) containing a solution of sodium hydroxide (1·06 g.) in water (2 ml.) gave β-2-*methylallyloxypropaldehyde* (51 g., 40%), b. p. 62°/9 mm., n_D^{20} 1·4352 (Found: C, 65·25; H, 9·7. $C_7H_{12}O_2$ requires C, 65·6; H, 9·45%). The 2 : 4-*dinitrophenylhydrazone* crystallised from 95% ethanol in long matted needles, m. p. 77—78° (Found: C, 50·25; H, 5·2; N, 18·2. $C_{13}H_{16}O_5N_4$ requires C, 50·65; H, 5·25; N, 18·2%); the *semicarbazone* crystallised from ethyl acetate–light petroleum (b. p. 40—60°) in fine needles, m. p. 110° (Found: C, 51·55; H, 7·95; N, 22·4. $C_8H_{15}O_2N_3$ requires C, 51·85; H, 8·15; N, 22·7%).

On hydrogenation in ethanol (100 ml.) over 5% palladium–charcoal (0·75 g.) at 20° and 750 mm. the aldehyde (12·2 g.) rapidly absorbed hydrogen (2420 ml., 1·01 mols.); absorption then ceased, and distillation of the filtered product gave β-iso*butoxypropaldehyde*, b. p. 65°/26 mm., n_D^{20} 1·4118 (Found: C, 64·5; H, 10·8. $C_7H_{14}O_2$ requires C, 64·6; H, 10·85%). The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous methanol in fine needles, m. p. 80° (Found: C, 50·8; H, 5·85; N, 17·8. $C_{13}H_{18}O_8N_4$ requires C, 50·3; H, 5·85; N, 18·05%), and the *semicarbazone* from ethyl acetate–light petroleum (b. p. 40—60°) (1 : 1, by vol.) in long fine needles, m. p. 118° (Found: C, 51·7; H, 9·0; N, 22·8. $C_9H_{17}O_3N_3$ requires C, 51·35; H, 9·15; N, 22·45%).

The authors are indebted to the Directors of the Distillers Co., Ltd., for permission to publish this note.

THE DISTILLERS CO., LTD., RESEARCH AND DEVELOPMENT DEPARTMENT,
GREAT BURGH, EPSOM, SURREY. [*Received, June 17th*, 1952.]

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784. *Dihalogeno-substituted Terephthalaldehydes and p-Tolualdehydes.*

By J. R. NAYLOR.

2 : 5-DIBROMO- AND 2 : 5-DICHLORO-TEREPHTHALALDEHYDES have been prepared by side-chain halogenation of the corresponding nuclear dihalogenated *p*-xylene, followed by hydrolysis of the product with concentrated sulphuric acid (Ruggli and Brandt, *Helv. Chim. Acta*, 1944, **27**, 274). The yields were not good, particularly that of the dichloro-compound. It is now shown that these compounds may be conveniently prepared, but not in good yield, by oxidation of the dihalogeno-substituted *p*-xylene, by means of chromium trioxide and sulphuric acid in the presence of acetic acid and acetic anhydride, to the corresponding terephthalaldehyde tetra-acetates (Thiele and Winter, *Annalen*, 1900, **311**, 359), from which the free aldehydes may be obtained in almost quantitative yield by hydrolysis with dilute sulphuric acid.

The previously unreported 2 : 5-dibromo- and 2 : 5-dichloro-4-methylbenzaldehyde diacetate are obtained as by-products of the oxidation. Hydrolysis of these compounds with dilute sulphuric acid gives the corresponding hitherto unknown benzaldehydes.

EXPERIMENTAL

M. p.s are uncorrected. Micro-analyses were carried out by Drs. Weiler and Strauss of Oxford.

2 : 5-*Dichloroterephthalaldehyde Tetra-acetate.*—2 : 5-Dichloro-*p*-xylene (32·7 g.) was dissolved in a stirred mixture of acetic acid (300 g.), acetic anhydride (600 g.), and sulphuric acid (90 g.) and cooled to 5°. Chromium trioxide (60 g.) was added at such a rate (2½ hours) as to keep the temperature of the cooled mixture between 5° and 12°. The mixture was stirred for a further 4 hours (10—15°), poured on crushed ice (5 kg.), and stirred overnight. The product (45·1 g.) was filtered off, and after recrystallisation from ethanol (1100 c.c.) gave 2 : 5-dichloro-terephthalaldehyde tetra-acetate (25·2 g.), m. p. 199·5—200° (37%) (Found: C, 47·6; H, 4·2; Cl, 17·25. Calc. for $C_{16}H_{16}O_8Cl_2$: C, 47·2; H, 3·9; Cl, 17·4%).

2 : 5-*Dichloroterephthalaldehyde.*—The foregoing tetra-acetate (43 g.) was added to a mixture of ethanol (250 c.c.), water (250 c.c.), and sulphuric acid (25 g.), heated under reflux for 1½ hours, and cooled. Filtration and recrystallisation of the product from aqueous ethanol gave 2 : 5-di-

chloroterephthaldehyde (18·4 g.), m. p. 157° (86%) (Found: C, 47·8; H, 2·2; Cl, 34·6. Calc. for $C_8H_4O_2Cl_2$: C, 47·3; H, 2·0; Cl, 35·0%).

2 : 5-*Dichloro*-4-*methylbenzaldehyde Diacetate*.—Concentration to 100 c.c. of the mother-liquor from the tetra-acetate gave 2 : 5-*dichloro*-4-*methylbenzaldehyde diacetate* (10·8 g.), m. p. 108° (20%) (Found: C, 49·9; H, 3·9; Cl, 23·9. $C_{12}H_{12}O_4Cl_2$ requires C, 49·5; H, 4·1; Cl, 24·4%).

2 : 5-*Dichloro*-4-*methylbenzaldehyde*.—The foregoing diacetate (8·7 g.) was treated as for the previous tetra-acetate but on a one-fifth scale and with 45 minutes' refluxing, giving the *aldehyde* (5·2 g.), m. p. 110·5—111° (91%) (Found: C, 51·1; H, 3·25; Cl, 37·2. $C_8H_6OCl_2$ requires C, 50·8; H, 3·2; Cl, 37·6%). Its 2 : 4-*dinitrophenylhydrazone* had m. p. 257° (Found: N, 15·5. $C_{14}H_{10}O_4N_4Cl_2$ requires N, 15·2%).

2 : 5-*Dibromoterephthalaldehyde Tetra-acetate*.—2 : 5-Dibromo-*p*-xylene (59 g.) was treated exactly as for the dichloro-analogue, but with 1·2-fold quantities. The product (56·5 g.) was filtered off and after recrystallisation from ethanol (4 l.) gave 2 : 5-dibromoterephthaldehyde tetra-acetate (33·6 g.), m. p. 218·5—219° (30·5%) (Found: C, 38·55; H, 3·05; Br, 32·5. Calc. for $C_{16}H_{16}O_8Br_2$: C, 38·7; H, 3·2; Br, 32·3%).

2 : 5-*Dibromoterephthalaldehyde*.—The tetra-acetate (4·9 g.) was treated as for its chloro-analogue, but on a one-fifth scale, giving 2 : 5-dibromoterephthaldehyde (2·7 g.), m. p. 189° (92%) (Found: C, 32·8; H, 1·9; Br, 54·35. Calc. for $C_8H_4O_2Br_2$: C, 32·9; H, 1·4; Br, 54·8%).

2 : 5-*Dibromo*-4-*methylbenzaldehyde Diacetate*.—Concentration to 100 c.c. of the mother-liquor from the tetra-acetate gave 2 : 5-*dibromo*-4-*methylbenzaldehyde diacetate* (13·5 g.), m. p. 117—117·5° (16%) (Found: C, 38·3; H, 3·3; Br, 41·6. $C_{12}H_{12}O_4Br_2$ requires C, 37·9; H, 3·2; Br, 42·05%).

2 : 5-*Dibromo*-4-*methylbenzaldehyde*.—The above diacetate (7·5 g.) was treated as for the dichloro-analogue (1 hour's refluxing), affording 2 : 5-*dibromo*-4-*methylbenzaldehyde* (5·2 g.), m. p. 142° (94%) (Found: C, 34·6; H, 2·3; Br, 58·5. $C_8H_6OBr_2$ requires C, 34·5; H, 2·2; Br, 57·6%). Its 2 : 4-*dinitrophenylhydrazone* had m. p. 265° (Found: N, 12·2. $C_{14}H_{10}O_4N_4Br_2$ requires N, 12·23%).

RESEARCH DEPARTMENT, THE CALICO PRINTERS' ASSOCIATION LTD.,
MANCHESTER. [*Received, June 26th*, 1952.]

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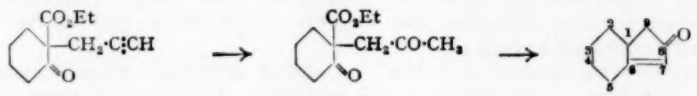
785. bicyclo[4 : 3 : 0]*Non*-6-*en*-8-*one*.

By A. M. ISLAM and R. A. RAPHAEL.

THE hitherto unknown *bicyclo*[4 : 3 : 0]non-6-en-8-one (III) has been synthesised in the following manner.



Reaction of the sodio-derivative of ethyl 2-keto*cyclo*hexane-1-carboxylate with propargyl bromide gave a good yield of the expected product (I), which with methanolic boron trifluoride in the presence of mercuric oxide (cf. Hamlet, Henbest, and Jones, *J.*, 1951, 2652) yielded the hydration product (II). Attempts to prepare (II) directly from ethyl 2-keto*cyclo*hexane-1-carboxylate and chloroacetone were unsuccessful under a variety of conditions, very small yields of impure products being obtained. When (II) was heated with dilute potassium hydroxide solution an intramolecular aldol-type condensation took place with concomitant hydrolysis and decarboxylation to furnish finally the required ketone (III).

EXPERIMENTAL

Ethyl 2-*Keto*-1-*propargyl*cyclo*hexane*-1-*carboxylate* (I).—A mixture of sodium ethoxide solution (from sodium, 1·7 g., and alcohol, 300 c.c.) and ethyl 2-keto*cyclo*hexane-1-carboxylate (12·5 g.) was heated under reflux for 30 minutes. Propargyl bromide (10 g.) was then added to the boiling solution during 1 hour and heating continued for a further 2 hours. Most of the

alcohol was removed, water (200 c.c.) was added, and the product isolated with benzene. Evaporation and distillation gave ethyl 2-keto-1-propargyl*cyclo*hexane-1-carboxylate as a colourless oil (12 g., 83%), b. p. 154°/12 mm., n_D^{19} 1·4590. In spite of the sharp b. p. a satisfactory carbon analysis for either this compound or its hydration product (II) could not be obtained. The *semicarbazone* crystallised from aqueous alcohol in colourless needles, m. p. 144° (Found: N, 15·7. $C_{13}H_{19}O_3N_3$ requires N, 15·8%).

Ethyl 1-*Acetonyl*-2-*keto*cyclo*hexane*-1-*carboxylate* (II).—A solution of the foregoing ester (7·3 g.) in methanol (15 c.c.) was added slowly to a catalyst solution prepared by warming together red mercuric oxide (0·5 g.), boron trifluoride–ether complex (0·2 c.c.), trichloroacetic acid (10 mg.), and methanol (1 c.c.). After the initial exothermic reaction was over, the mixture was shaken at room temperature for 2 hours and then poured into dilute sulphuric acid. Isolation by means of ether, evaporation, and distillation gave the required diketone (II) as a pale yellow oil (6 g., 75%), b. p. 144°/1 mm., n_D^{19} 1·4504. The *disemicarbazone* crystallised in plates, m. p. 214°, from aqueous alcohol (Found: N, 24·9. $C_{14}H_{24}O_4N_6$ requires N, 24·8%).

bicyclo[4 : 3 : 0]*Non*-6-*en*-8-*one* (III).—The 2-acetonyl compound (3 g.) and aqueous potassium hydroxide solution (5%; 150 c.c.) were heated under reflux for 6 hours under nitrogen. After being cooled, the mixture was acidified with dilute sulphuric acid and the product isolated with ether. Evaporation and distillation gave bicyclo[4 : 3 : 0]*non*-6-*en*-8-*one* (1·3 g., 73%) as a colourless oil, b. p. 88°/4 mm., n_D^{19} 1·5190 (Found: C, 79·1; H, 8·9. $C_9H_{12}O$ requires C, 79·4; H, 8·8%). Light absorption in ethanol: $\lambda_{max.}$ 2280 (ε = 16,500) and 2860 Å (ε = 140) [Acheson and Robinson, *J.*, 1952, 1131, record $\lambda_{max.}$ 2250 Å (ε = 18,150) for 3-methyl*cyclo*pent-2-enone]. The 2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 200°, from alcohol (Found: C, 57·0; H, 4·9; N, 18·1. $C_{15}H_{16}O_4N_4$ requires C, 56·9; H, 5·1; N, 17·7%). Light absorption in ethanol: $\lambda_{max.}$ 2580 (ε = 19,000) and 3900 Å (ε = 26,500). The *semicarbazone* crystallised from alcohol in leaflets, m. p. 224° (Found: N, 21·5. $C_{10}H_{15}ON_3$ requires N, 21·7%).

We are indebted to the Chemical Society for a Research Grant.

THE UNIVERSITY, GLASGOW, W.2. [*Received, June 27th*, 1952.]

OBITUARY NOTICE.

ALFRED FRANCIS JOSEPH.

1881—1951.

ALFRED FRANCIS JOSEPH was born in London on May 9th, 1881, and died at Truro on October 5th, 1951. Brought up in the Jewish faith, he matriculated in 1899 and was registered as an internal student at Birkbeck Institution (now Birkbeck College) in 1901 but transferred to the Royal College of Science in 1902. He was awarded 1st class honours at the Bachelor of Science Examination in 1904. During these years he came under the influence of such men as Professor John Perry, Sir H. E. Armstrong, Professor H. L. Callendar, and Sir William Tilden. His first paper, written in collaboration with J. E. MacKenzie, appeared in the *Transactions* in 1904. Two years later the same journal had Joseph's paper on The Reciprocal Displacement of Acids in Heterogeneous Systems. This was followed by a Note on the Estimation of Iron in Ferric Solution and by a short paper on the Estimation of Formic Acid : both of these appeared in the *Journal of the Society of Chemical Industry*, 1910, the latter paper being communicated from the Ceylon Medical College in Colombo.

After teaching for two years at Wimbledon College, a Roman Catholic Institution, Joseph had gone to Ceylon in September 1906 to take up the post of Science Master in the Royal College, which he left in January 1908 to become Professor of Chemistry at the Ceylon Medical College which now forms part of the University of Ceylon. Here he was able to introduce Studentships for men in training as teachers of science; he published a text book on Practical Chemistry, and maintained a steady stream of research work. Much of this consisted in Experimental Investigations on the Properties of Bromide Solutions and this became the title of a thesis for which Joseph received the Degree of Doctor of Science in chemistry from the University of London in 1916.

From 1915 to 1917 Joseph was acting Registrar of the Ceylon Medical College. He left Ceylon in 1917 to enter the Ministry of Munitions of War. In association with Professor T. M. Lowry and Professor E. N. da C. Andrade he worked in London during the latter part of the war on problems concerned with shell filling. He had to visit the United States in connection with these duties and remained indifferent to danger from submarine attack owing as he said to his more immediate concern with sea sickness.

After the war Joseph became Government Chemist in the Anglo-Egyptian Sudan. During the period 1920—1929 he built up a small team of research chemists whose work was mainly directed to a new field of work, the assessment and solution of problems arising from irrigation of the alkaline and somewhat saline clay of the Sudan Gezira. This enterprise, involving an investment exceeding £20 million and forming an important experiment in co-partnership, met with difficulties which, in due course, were overcome. The good repute of agricultural research in the Sudan is due in part to Joseph's insistence on high professional standards both in recruitment of staff and in output of publishable work. He was instrumental also in bringing to the Sudan the latest techniques in agricultural experimentation by promoting successive visits by Sir John Russell, E. M. Crowther, and F. G. Gregory. Joseph's own work in soil science gained immediate international recognition : many technical papers were published though it must be admitted that the Publication Committee of the Chemical Society soon refused to accept any more articles on the composition and properties of clay.

In 1929 Joseph left the Sudan and under Sir John Russell started the Imperial (now the Commonwealth) Bureau of Soil Science. In this case also his outspoken, austere, but not ill-natured, rejection of second-rate work set within two years the high standard that the Bureau has since so successfully maintained.

In 1931 Joseph gave up the scientific work in which he had been continuously successful and began to study for the Anglican Ministry. He was ordained priest on Trinity Sunday 1933 and in 1937 was admitted to the Society of St. John the Evangelist, better known as the Cowley Fathers. After his ordination and religious profession he became well versed in Theology and liturgical matters. Besides being Superior of St. Edward's House in Westminster he was for several years Deputy Assistant General of the Society and sub-warden of the Fellowship of St. John. Members of the Fellowship in every part of the country have often spoken most warmly of the unsparing help he has given them. By his wise counsel he gave much help to various communities. Shortly before he died he became Secretary to the Advisory Council for Religious Communities in the Anglican Church.

Joseph married in Colombo Miss Ida Guinivere O'Donoghue, B.Sc., eldest daughter of the Rev. E. G. O'Donoghue, a clergyman-historian in his day. Most unfortunately she died of enteric about six months later. Her influence remained evident throughout the following 44 years of Joseph's life.

H. GREENE.

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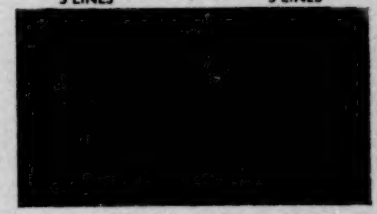

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